COMPARATIVE STUDY OF HALOBETASOL AND TACROLIMUS IN TREATMENT OF LICHEN PLANUS

Dissertation Submitted in
fulfillment of the university regulations for

MD DEGREE IN
DERMATOLOGY, VENEREOLOGY AND LEPROSY
(BRANCH XII A)

Madras Medical College
Chennai

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
CHENNAI

APRIL 2011

CERTIFICATE

Certified that this dissertation entitled ***"COMPARATIVE STUDY OF HALOBETASOL AND TACROLIMUS IN TREATMENT OF LICHEN PLANUS "*** is a bonafide work done by **Dr.VIDHYA RAVINDRAN,** Post Graduate Student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2008 – 2011. This work has not previously formed the basis for the award of any degree.

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SPECIAL ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr.J.MOHANASUNDARAM, M.D**.,**PhD,DNB** Dean, Madras Medical College for allowing me to do this dissertation and utilize the institutional facilities.

ACKNOWLEDGEMENT

This study which has been an integral part of my stay in the Department of Dermatology, Madras Medical College, Chennai wouldn't have been completed without the help of great number of people. It gives me great pleasure in thanking them in the beginning.

In the first place, I express my sincere gratitude to **Prof. Dr.D.PRABHAVATHY, M.D.,D.D.,** Professor and Head, Department of Dermatology and Leprology and my co-ordinator for her invaluable guidance, motivation and help throughout the study. I would like to express my sincere and heartfelt gratitude to **Dr.P.ELANGOVAN, M.D.,D.V.,** Director In charge, Institute of Venereology for his guidance.

I express my earnest gratitude to **Dr.S.V.Somasundaram, M.D.,D.D.,** Professor and Head, Department of Occupational Dermatology and Contact Dermatitis for his constant motivation and guidance. I thank **Dr.S.Nirmala, M.D.,D.D.,** Additional Professor, Department of Occupational Dermatology and Contact Dermatitis for her benevolent help and support.

I am grateful to **Dr.S.Jayakumar, M.D.,D.D**., Additional Professor, Department of Dermatology for his invaluable guidance and

help. I sincerely thank **Dr.R.Arunadevi, MD.,DD**.**,** Additional Professor (Leprosy)for her priceless support. I humbly thank **Dr.C.Janaki, M.D.,D.D.,** Additional Professor of Dermatology (Mycology) for her valuable guidance throughout my work and for her constant support and motivation.

I wish to thank **Dr.B.Parveen, M.D.,D.D.**, Former Professor, Department of Dermatology and **Dr.K.Gajendran, M.D.,D.V.**, Former Director, Institute of Venereology for their constant support and motivation.

I express my sincere gratitude to **Dr.Jayakumari Jeevan, M.D.,D.D.,** Former Professor of Leprosy for her support.

I humbly thank my Guide **Dr.Samuel Jeyaraj Daniel M.D., (DVL),** Assistant professor for his valuable guidance throughout my work. His support and timely suggestions from the beginning of the study to the end has been of immense help.

My sincere thanks go to **Dr.S.Kumaravel M.D,D.D.**, **Dr. J.Manjula M.D.,DNB., Dr.V.Anandan M.D.,(Derm),DCH.,DNB., Dr. G.K.Tharini,M.D**, **Dr.N.Hema, M.D.,(DVL), Dr.Madhu, M.D.,DCH.,** and **Dr.S.Anupama Roshan, D.D.V.L**., Assistant

professors Department of Dermatology for their kind support and encouragement.

I thank **Dr.A.Hameedullah., M.D.,** and **Dr.Afthab Jameela Wahab M.D.,D.D**., Assistant Professors, Department of Occupational Dermatology and Contact Dermatitis for their support and help.

I am inclined to thank **Dr.V.Thirunavukarasu, M.D.,D.V**., **Dr.K.Venkateswaran, M.D.,D.V.**, **Dr.P.Mohan, M.D.,D.V.**, **Dr. S. Thilagavathy M.D.,D.V., Dr.S.Arunkumar M.D.,D.V**., **Dr.S.Kalaivani, M.D.,D.V.**, **Dr. Ahmed Shariff M.D.,(DVL).,** and **Dr.P.Prabahar, M.D.,(DVL), Dr.S.Saravanan, M.D.,(DVL)., DCH.,** Assistant Professors, Department of Venereology, for their help and suggestions.

This acknowledgement can't be complete without thanking my colleagues for being instrumental at crucial junctures. I duly acknowledge the paramedical staff for their help and favors.

The study would have never been possible but for the participation of the subjects who willingly participated in my research. I am extremely grateful to them for being part of the study.

I wish to thank and give homage to our beloved Former Additional Professor **Late Dr.N.Kumar M.D.,D.V.,D.M.R.D.,** and **Late Dr.V.Thirunavukarasu M.D.,D.D.,** for their moral support.

Constraint of space may have led to few names gone missing in my acknowledgement. I wish to express sincere gratitude to all those who have been associated with my study and have helped me in bringing this dissertation to this form.

CONTENTS

INTRODUCTION

Lichen Planus is one of the most itchy dermatoses. It is prevalent worldwide with no social or climatic predilection. It affects the skin, mucous membrane, nails and hair. Itching is a constant feature of lichen planus and the lesions heal with pigmentation which may be persistent and intense in dark skinned people. Spontaneous remissions can occur after varying amounts of time.

An autoimmune mechanism has been proposed with the involvement of activated T cells directed against an unknown antigen in the skin or mucosa. Certain infections have also been associated with lichen planus but the cause and effect relationship remains controversial.

There are no evidence-based recommendations for the treatment of lichen planus. Many of the recommendations of the experts are based on their personal experience. Most of the published trials are observational and are not always prospective. Only a few randomized controlled trials have been performed. However treatment with medium to high-potency topical corticosteroids is generally recommended as the first-line therapy for localised lichen planus.

Topical Tacrolimus, a calcineurin inhibitor is used extensively in the treatment of atopic dermatitis. Unlike topical corticosteroids, it does not cause skin atrophy. Topical Tacrolimus in addition to its inhibitory effect on cytokine production causes alterations in epidermal antigen-presenting dendritic cells that may result in decreased immunologic response to antigens. Topical tacrolimus has been used in oral lichen planus but to our knowledge not in cutaneous lichen planus except for a single case report.

The possible role of activated T cells in the pathogenesis of lichen planus as well as the extensive safety profile makes topical tacrolimus an attractive option for the treatment of cutaneous lichen planus. However there are no head to head comparisons of corticosteroids and tacrolimus in the treatment of lichen planus.

Towards this goal we performed a prospective, randomised, open label clinical trial comparing the therapeutic efficacy of a topical corticosteroid 0.05% halobetasol propionate with a topical calcineurin inhibitor 0.1% tacrolimus in adults with localised cutaneous lichen planus.

REVIEW OF LITERATURE

TERMINOLOGY:

Lichen planus is a unique inflammatory disorder characterized by flat–topped, polygonal, violaceous papules in the skin. It also affects the mucous membrane, nails and hair follicles.

LICHEN PLANUS is derived from the Greek word “Leichen” meaning “tree moss” and the Latin word “planus” meaning “flat”. The appearance of lichen planus has been likened to the scurfy, finely furrowed dry excrescences of the symbiotic vegetation known as lichen[1].

The term “lichenoid” is used by clinicians to describe flat – topped, shiny papular eruptions resembling lichen planus or by histopathologists to describe a type of tissue reaction consisting principally of basal cell liquefaction and a band like inflammatory infiltrate in upper dermis[2].

HISTORY:

- The term ‘lichen planus’ was introduced by William James Erasmus Wilson in 1869 to describe the condition which had been previously named ‘lichen ruber’ by Hebra[3].

- Louis Fredric Wickham described the characteristic striae on lichen planus lesions in 1895.

- The histological findings were defined by Darier in 1909[4].

- Graham Little described scalp involvement in 1919.

PATHOGENESIS

LP is thought to be an immunologically mediated disorder[5] where $CD8^+$cytotoxic T cells recognize an antigen (currently unknown) associated with the MHC class I on lesional keratinocytes and lyse them[6]. CD4 + and CD8+ T cells are found in the lesional skin of lichen planus. With disease progression, majority of lymphocytes in the infiltrate of lichen planus are CD8+ and CD45 RO (memory) cells & express the αβ T–cell receptor and in a minority, the γ-δ receptor (which is not normally found in healthy skin). CD8+ cells are responsible for development of apoptosis. T helper cells may also become activated, via antigen presenting cells such as langerhans cells or epidermal keratinocytes in association with MHC class II and specific cytokines. The T helper lymphocytes may propagate CD8+ cytotoxic lymphocytes through cellular co-operation & release of cytokines.

The epithelial-lymphocyte interaction can be divided into 3 stages.

1. Antigen recognition 2. Lymphocyte activation 3. Keratinocyte apoptosis[1].

1. Lichen planus – specific antigen recognition:

The nature of the antigen is unknown. It may be an auto reactive peptide or an exogenous antigen such as an altered protein, drug, contact allergen, viral or infectious agent, or an unidentified immunogenic target[7]. It may act as a hapten to initiate the process.

2. Cytotoxic T – Lymphocyte Activation

Following antigen recognition, CD8 + T cells are activated and undergo lesional tissue clonal expansion, leading to oligoclonal & occasionally monoclonal proliferation. Activated lymphocytes (both helper and cytotoxic) release cytokines such as IL-2, IL–4, IL–10, IFN–γ, TNF-α and TGFβ, that attracts lymphocytes to the epithelium & regulates their activity. The balance between lymphocyte activation and downregulation determines the clinical disease.

IFN–γ produced by the T helper cells i) induces keratinocytes to produce lymphotoxin α and TNF-α & to upregulate MHC class II thus increasing interactions with CD4 + T cell ii) upregulates expression of ICAM–1 & VCAM–1 by basal keratinocytes, langerhans cells and other macrophage dendritic cells.

Laminin 5 & collagen IV, VII are increased in lichen planus lesions and act as ligands for β_1 integrin present on surface of lymphocytes thus facilitating attachment of lymphocytes with the basement membrane. Integrin α3, present on activated skin homing T cells may localize the cells to the epidermal–dermal interface & basement membrane, which contains epiligrin/laminin–5, a ligand for this integrin[8]. This close interaction between the lymphocytes and basement membrane, activates matrix metalloproteinase-9 (MMP-9) produced by lymphocytes resulting in apoptosis, basement membrane disruption, duplication & subepidermal cleft formation.

Keratinocytes produce IL-1β, IL-4, IL-6, GM-CSF, TNFα, which further activates tissue macrophages & peripheral blood mononuclear cells and upregulates cell surface adhesion molecules & migration activity.

3. Keratinocyte Apoptosis

Possible mechanisms for keratinocyte apoptosis are 1) T cell secreted TNFα binding to TNFαR1 receptor on the keratinocyte surface 2) T cell surface CD95L (Fas ligand) binding to Fas on the keratinocyte 3)T cell secreted granzyme B / perforin entering the keratinocytes by inducing pores: all these activiate the caspase cascade resulting in apoptosis of the keratinocytes[7].

T cell secreted MMP–9 disrupts the basement membrane, thus blocking the cell survival signals to the keratinocytes & loss of this anti-apoptotic mechanism induces apoptosis.

GENETICS

There may be a genetic predisposition to develop lichen planus. Associations with HLA–3 & HLA–5[9], HLA–B7[10], HLA–28 with carbohydrate intolerance, HLA–DR1, HLA-DR10 and HLA-DRB1*0101 have been reported. HLA–B8 is more common in patients with oral lichen planus and HLA–BW35 is strongly associated with cutaneous lichen planus[1]. A familial form of the disease exists[11] and monozygotic twins may be affected[12].

VIRUSES

HCV RNA has been isolated from lesional skin in patients with lichen planus & chronic HCV infection[13]. Thus, an HCV related product has been postulated as a possible antigen in lichen planus. Lichen planus has been associated with human herpes virus type 7 replication[14].

DENTAL AMALGAMS:

The presence of amalgam or gold is not associated with an increased risk of oral LP, but corrosion of amalgams, and a 'galvanic effect' from dissimilar dental materials in continuous contact with the mucosa (bimetallism) is associated with elevated risk of oral LP[15].

MISCELLANEOUS CAUSES

LP has been induced by radiotherapy[16]. Anxiety, depression[17] and stress[18] may be risk factors for developing lichen planus.

EPIDEMIOLOGY

LP has a worldwide distribution with no racial predisposition. 0.22% to 1% of adult population is affected by cutaneous LP[3].The incidence in India is 0.38%[19].There is no sexual predilection[1]. Average

age of onset is the 4th decade in males and 6th decade in females[3]. Association of lichen planus with blood group A has been proposed[20].

CLINICAL FEATURES

MORPHOLOGY

Lichen planus is characterized by shiny, violaceous, flat-topped polygonal papules, varying in size from a pin–point to several centimeters. The 4 Ps– purple, polygonal, pruritic, papule are used to describe the clinical appearance of the lesions. White lines known as Wickham's striae may traverse the surface of the papules, and are better visualized with a hand lens after applying oil, water or xylene. In the acute and evolving stages of the disease scratching, injury or trauma may induce an isomorphic response (Koebner response)

SITES

Lichen planus can affect any part of the body, but is most often seen on the volar aspect of the wrists, lumbar region, and around the ankles. The arms, legs, thighs, lower back, trunk, neck, oral cavity, genitalia, scalp, nails may also be affected. Face is usually spared in classical cases and palmoplantar involvement is unusual.

SYMPTOMS

Itching is a constant feature and ranges from mild to continuous severe itching. Hypertrophic lesions usually have severe itching. Often, there is no evidence of scratching as the patient rubs, rather than scratches to gain relief.

Erosive lichen planus of the oral cavity can cause extreme pain. Patients with oral lesions may complain of discomfort, stinging or pain.

NATURAL HISTORY

The onset is usually insidious. The papules are first erythematous and turn violaceous after a few weeks. The papules eventually flatten after a few months and are replaced by an area of hyperpigmentation that retains the shape of the lesion that persists for months or years. The pigmentation may be intense in dark skinned individuals.

New papules may continue to erupt. Some papules persist, enlarge & thicken to develop a roughened surface with prominent violaceous hue (hypertrophic LP). Lesions resolve with atrophy & scarring.

CLINICAL VARIANTS

Variations can occur in the clinical presentation and may be categorized according to

1) The configuration of lesions 2) the morphology 3) the site of involvement.

CONFIGURATON OF LESIONS

(i) Annular lichen planus:

They may be formed (i) either by groups of papules arranged in rings or (ii) by single, large papules clearing in the centre leaving behind an active margin. They are most commonly seen over the penis.

(ii) Linear Lichen Planus

It constitutes 0.25% of the different clinical patterns[21]. Papules may develop in a linear pattern secondary to trauma (Koebnerisation). Sometimes, linear lesions follow a segmental / zosteriform pattern or lines of Blaschko[22].

MORPHOLOGY OF LESIONS

(i) Hypertrophic Lichen Planus / Lichen Planus Verrucosus):

Extremely pruritic, thick raised verrucous plaques are seen primarily on the shins and around the ankles. The lesions tend to be chronic and some lesions show central depigmentation surrounded by a hyperpigmented rim. They heal with hypo or hyperpigmentation & scarring. There are reports of Squamous Cell Carcinoma arising from long–standing lesions of hypertrophic LP[23].

(ii) Atrophic Lichen Planus: Well demarcated papules or plaques with central atrophy are seen. Atrophy may result from faded annular lesions or resolved hypertrophic lesions especially on the lower legs.

(iii) Vesiculobullous Lichen Planus:

This is characterized by the development of vesicles and bulla within the lesions of lichen planus. They may suddenly appear during an acute flare–up of the disease.

(iv) Lichen Planus Pigmentosus:

This is a pigmentary disorder seen in India and the Middle East. Slate grey or brown macules are seen over the sun-exposed areas and the flexural folds[24]. Pigmentation may be diffuse, reticular, blotchy, or perifollicular. The mucous membranes, palms and soles are usually not involved and there may or may not be associated lichen planus papules.

(v) Actinic Lichen Planus (Lichen planus subtropicus / Lichen planus tropicus / Lichen planus Actinicus / Lichen Planus Atrophicus Annularis / Summertime Actinic lichenoid eruption / Lichenoid melanodermatosis).

This is generally seen in children or young adults living in tropical countries. Lesions occur over the sun-exposed areas (usually face), as well–defined annular or discoid patches, with a deeply hyperpigmented center surrounded by a hypopigmented zone.

(vi) Guttate Lichen Planus

Lesions are discrete, widely scattered, ranging from 1-2 mm to 1 cm.

(vii) Follicular Lichen Planus (Lichen planopilaris / Lichen planus follicularis / Lichen planus peripilaris / Lichen planus acuminatus)

Individual keratotic follicular papules are seen predominantly over the scalp. It may also involve the trunk, medial aspect of the proximal extremities and may occur alone or in association with other forms of lichen planus. Cicatricial alopecia may develop over the scalp.

viii) Erosive / Ulcerative lichen planus

Here, chronic painful ulcerations develop over the feet leading to atrophic scarring & permanent loss of nails.

SITE OF INVOLVEMENT

(i) LP involving the mucous membranes: Lichen planus can affect the mucosa of the mouth, vagina, oesophagus, conjunctiva, urethra, anus, nose & larynx. Lesions confined to the mouth comprise 15% of all cases [25]. Different types include reticulate, atrophic, erosive, papular, ulcerative & bullous forms.

In males, genitalia is involved in 25% of cases & glans penis is the most common site followed by penile shaft & scrotum[1]. In females,

genital involvement consists of leukoplakia or erythroplakia , sometimes with erosions and sometimes as a generalized desquamative vaginitis. The association of erosive LP of the vulva & vagina with desquamative gingivitis is called as the vulvovaginal gingival syndrome[26].

ii) Lichen Planus of the Nails: Nail involvement occurs in 10–15% of patients[27].Lichen planus can affect both the matrix & the nailbed. Nail matrix involvement results in thinning, longitudinal ridging, onychorrhexis, fissuring, trachyonychia, dorsal pterigium formation (classical finding of LP). Lichen planus of the nailbed may give rise to longitudinal melanonychia[28], hyperpigmentation, subungual hyperkeratosis and onycholysis.

'Pup tent' sign is due to papules on the nail bed which lift the nail plate resulting in longitudinal splitting of the nail plate. Pterigium results from a focal destruction of the nail matrix with subsequent scar formation & attachment of proximal nail fold to the nail plate.

iii) LP of the palms & soles: They lack the characteristic shape & colour and are firm, yellow papules occurring in broad sheets or as punctuate keratosis[29]. Itching may be absent. Vesicle – like papules[30] have also been recorded. Ulceration can occur especially over the soles.

iv) Inverse lichen planus: This consists of reddish brown, discrete papules & nodules distributed over the axillae, infra–mammary areas, groins and antecubital & popliteal areas.

SPECIAL FORMS OF LICHEN PLANUS

(i) Lichen planus pemphigoides: Lichen planus is acute, generalized and is followed by sudden appearance of large bullae in both involved and involved skin.

(ii) LP / LE Overlap syndrome: It is a rare variant, with lesions that share features of lichen planus and lupus erythematosus. Atrophic plaques and patches with hypopigmentation and red to blue–violet colour with telangectasia & scaling are characteristic and are most common over the extremities.

OTHER VARIANTS

(i) Perforating Lichen Planus: Hanau & Sengel[31] have described a perforating variant of lichen planus over the buttocks & volar surfaces of the wrist which showed transepidermal elimination of colloid bodies on histopathology.

(ii) Exfoliative Variant: Lichen planus lesions involve more than 90% of the body with increased scaling.

(iii) Lichen Planus "Invisible De Gougerot"[1]: Here, only pruritus is present and lesions are not visible under naked eye, but become apparent with woods lamp examination. Biopsy shows lichenoid histology.

ASSOCIATED CONDITIONS

a) Autoimmune disorders: Alopecia Areata, diabetes mellitus, vitiligo, dermatomyositis, morphea, lichen sclerosus, systemic lupus erythematosus, pemphigus, paraneoplastic pemphigus, thymoma, myasthenia gravis may be associated with lichen planus.

b) Infections: Association of lichen planus with syphilis, hepatitis C, herpes simplex virus, amoebiasis, chronic bladder infections has been reported[3]. HIV has also been implicated in triggering lichen planus[32]. Several reports described lichen planus like eruptions after hepatitis–B vaccination[33].

c) Liver disorders: Autoimmune chronic active hepatitis, primary biliary cirrhosis and post viral chronic active hepatitis[34] are associated with increased frequency of lichen planus.

d) Miscellaneous:A high prevalence of anti-cardiolipin antibodies have been documented in patients with HCV associated oral lichen planus[35]. Lichen planus has occurred in patients with Castleman's tumor[36], in certain tattoo reactions, in areas where coexisting mercury hypersensitivity to the injected dye exists[37].

SYNDROMES ASSOCIATED WITH LICHEN PLANUS

1) ***Graham–Little–Piccardi–Lassueur Syndrome***: triad of follicular LP of the skin, cicatricial alopecia of the scalp and non-scarring alopecia of the axillary/pubic hair.

2) ***Grinspan Syndrome***: oral lichen planus with diabetes mellitus and essential vascular hypertension.

3) ***Jolly's Syndrome*** : association of oral LP with diabetes mellitus.

4) ***Vulvovaginal Gingival Syndrome of Hewitt and Pelisse***

COMPLICATIONS

1) Cicatricial alopecia

2) Permanent loss of nails

3) Ulcerative / atrophic/ plaque forms of oral lichen planus, vulval lesions and hypertrophic lesions[23] have a potential to develop into SCC.

4) Cicatricial conjunctivitis[38] and lacrimal canalicular obstruction[39]

DIAGNOSIS

The classical lesions of lichen planus present no difficulty in diagnosis. In lesions with varied morphology, clinical picture along with biopsy provides the diagnosis.

HISTOPATHOLOGY[40]

The classical histopathological features of lichen planus, seen in fully developed LP papules are

i) **Hyperkeratosis**: Compact orthokeratosis

ii) **Focal hypergranulosis**: Uneven and wedge shaped thickening of granular layer. Wickham's striae are caused by focal increase in thickness of the granular layer.

iii) **Irregular acanthosis**: giving rise to saw–toothed appearance.

iv) **Hydropic degeneration of the basal cell layer**

v) **Band like inflammatory infiltrate** consisting of lymphocytes and macrophages seen in papillary dermis abutting the epidermis. Macrophages are seen in the upper dermis due to pigment incontinence.

vi) **Colloid bodies** (Hyaline / cytoid / civatte bodies): They are found singly or in clumps & are transformed degenerating basal epidermal cells.

Max Joseph space (Caspary Joseph space)

Small areas of artefactual separation between the epidermis & dermis, known as Max–Joseph spaces are seen[41]. Sometimes, extensive damage to the basal cells results in formation of sub-epidermal blisters due to massive separation. Earliest finding is the increase in langerhans cells[42] associated with a perivascular inflammatory infiltrate.

Oral Lichen Planus: Lesions show parakeratosis without a granular layer. Epithelium is atrophic & ulcerations may be seen.

Lichen Planopilaris: Early lesions show a focally dense, band–like perifollicular lymphocytic infiltrate at the level of the infundibulum & isthumus. Vacuolar changes of the basal layer of outer root sheath and necrotic keratinocytes are seen. Follicular plugging is present. Interfollicular epidermis is spared.

In late lesions, there is perifollicular fibrosis and epithelial atrophy giving rise to a HOUR GLASS configuration.

Ulcerative LP : Skin adjacent to the ulcer shows changes of established lichen planus.

Lichen Planus Actinicus: A histologic picture comprising of

a) a form with features comprising of classical LP, with thinning of the epidermis in the center of the lesions with more evidence of pigmentary incontinence b) an intermediate form (lichenoid melanodermatitis) with foci of spongiosis and parakeratosis c) a more eczematous type [43].

LP / LE Overlap Syndrome: histology and immunofluroscence may show features of lichen planus or lupus predominantly or both may coexist.

Lichen Planus Pemphigoides: Biopsies from blisters on uninvolved skin show subepidermal bulla with an infiltrate that is not band like and which contains eosinophils.

ELECTRON MICROSCOPY

Basal keratinocytes together with desmosomes and hemidesmosomes show degenerative changes. Necrotic keratinocytes contain cell organelles such as melanosomes and mitochondria, and rarely, nuclear material.

The dermal infiltrate, which extends to the epidermis,causes fragmentation followed by duplication & irregular folding of the lamina densa. Some lymphocytes have convoluted nuclei similar to sezary cells.

DIRECT IMMUNOFLUROSCENCE

Apoptotic keratinocytes identified by globular deposits of IgM, IgG & IgA, are seen in large numbers or in clusters in the lower epidermis surrounding the DEJ. Shaggy deposits of fibrinogen at the DEJ is characteristic of lichen planus .

In lichen planus pemphigoides, DIF of perilesional lesion shows IgG and C3 in linear arrangement along the basement membrane zone .In immunoelectron microscopy, C3 is localized to the lamina lucida as in bullous pemphigoid.

TREATMENT

Different treatment modalities are in use for lichen planus. A large number of drugs have been tried topically and systemically and corticosteroids remain the most effective treatment. Oral anti-histamines are useful for alleviating pruritus. Many of the advocated treatments lack conclusive evidence for efficacy[44]

General measures:

Avoiding the exacerbating drugs, minimising trauma to skin and mucosa are recommended. For oral lichen planus, good oral hygiene should be maintained and dental care should be instituted.

Current drugs in treatment of lichen planus:

They can be classified into 1) Topical 2) Intralesional 3) Systemic

Topical steroids

Topical corticosteroids are the most commonly used drugs in the treatment of lichen planus.

History:

In 1952, Sulzberger and Whitten were the first to use hydrocortisone in the treatment of eczematous dermatitis. Their success marked a corner stone in dermatology.

Mechanism of Action:

Topical corticosteroids exert their effects through direct and indirect mechanisms which are mediated through the Glucocorticoid Receptor(GCR)

The GCR belongs to the superfamily of nuclear receptors. It is widely distributed in almost all cells. The receptor is found as a component of a heterotetrameric structure containing 2 molecules of 90 kDa heat shock protein hsp 90,and a 59 kDa protein p59 which belongs to the family of immunophilins. The cellular events that take place are

1) The corticosteroid diffuses into the target cell and binds to the GCR-alpha in the cytoplasm
2) Receptor-ligand interaction results in activation of the receptor and dissociation from other components of the complex.
3) Activated receptor with the ligand translocates to the nucleus and interacts with the specific response elements in the genome, glucocorticoid response elements (GRE) which results in modulation of transcription of various genes resulting in diverse cellular effects.
4) The metabolic effects are brought about by transcription and the anti-inflammatory effects are brought about by trans-repression. It

may inhibit directly or indirectly the activity of other transcription factors including NF- κB,AP-1,NFAT.

The effects are

i) Anti-inflammatory

a) Direct effects:

1) Stabilisation of lysosomal membranes and cell membranes
2) Inhibition of mast cell stimulation by IgE
3) Inhibition of release of histamine and other mast cell mediators

b) GCR mediated effects (delayed)

Induction of anti-inflammatory proteins – lipocortin, vasocortin and vasoregulin

Lipocortins inhibit phospholipase A_2 and block release of arachidonic acid and PAF from cell membranes preventing formation of prostaglandins

Vasocortin and vasoregulin decrease vascular permeability.

ii) Immunosupressive:

a) Polymorphonuclear leucocytes:

Decreased adherence to the vascular endothelium, decreased migration to sites of inflammation, decreased phagocytosis

b) Monocytes:

Decreased chemotaxis and decreased fungicidal activity

c) Lymphocytes:

Decreased antibody dependant cellular cytotoxicity and NK cell activity

d) Langerhans cells:

1) *Superpotent TCS:* loss of cells expressing Langerhans cell markers(CD1a).

2) *Moderate potency steroids:* decreased expression of Fc receptor, C3b receptor, and HLA DR positivity,but no alteration in CD1a antigen expression.

iii) Vasoconstrictive effects:

1. Potentiation of vascular response to catecholamines

2. Reduction of vascular smooth muscle sensitivity to histamine and bradykinin

iv)Anti-proliferative effects:

1. Epidermis: reduction of mitotic activity in the epidermis leading to reduction of stratum corneum thickness, granular layer[45], flattening of the basal cell layer, inhibition of pigment production by the melanocytes.

2. **Dermis:**

Early atrophy: results from the reduction in dermal volume due to reduced water content and loss of glycosaminoglycans, hypoactive fibroblasts

Late atrophy: results from the abnormal aggregation and reduction of collagen and elastic fibres. Dermal vessels become fragile due to loss of fibrous and ground substance support.

Potency ranking of topical corticosteroids

The ability of a given corticosteroid agent to cause vasoconstriction usually correlates with its anti inflammatory potency, and thus vasoconstrictor assays are used to predict the activity of an agent. The most commonly used test is the Stoughton vasoconstriction assay.

Topical corticosteroids have been divided into seven classes based on their potency, from super potent steroids in class 1 to least potent in class 7(American classification).

Adverse Effects:

Local as well as systemic adverse effects have been documented with the use of topical corticosteroids under normal conditions, 99 % of the applied topical steroid is removed from the skin and only 1% is therapeutically active. Cutaneous adverse effects can result from the small percentage of percutaneously absorbed corticosteroid or from its transient presence on the skin.

Local Adverse Effects:

The most common local adverse effect of topical corticosteroids is atrophy[46]. This results in shiny wrinkled fragile skin, prominent

vasculature, stellate pseudoscars, purpura, easy bruising, ulceration and striae. Atrophy of the epidermis maybe seen within two weeks of daily use of super potent topical corticosteroids without occlusion[47] or within one week with occlusion[48].

The other adverse effects seen with usage of topical corticosteroids are impaired wound healing, contact dermatitis, facial hypertrichosis, folliculitis, miliaria, increased susceptibility to bacterial, fungal and viral infections (crusted scabies, tinea incognito, infantile gluteal granuloma), perioral dermatitis, rosacea, acneiform eruption, steroid rebound, glaucoma and cataracts (when used around the eyes) and tachyphylaxis.

Systemic Adverse Effects:

Topical corticosteroids can be absorbed percutaneously in significant quantities to cause systemic adverse effects. These include suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, hyperglycemia, intracranial hypertension, growth retardation in children, reduced bone mineral density, edema, hypocalcemia, hypertension, cataract formation, glaucoma development and peptic ulcer.

Contra Indications:

1. *Absolute* – History of hypersensitivity to the topical corticosteroid or a component of the vehicle.

2. *Relative* – Untreated local bacterial, fungal, viral or mycobacterial infection, infestation and ulceration.

Dosing Regimen:

As a working rule, not more than 45gm/week of potent topical corticosteroids or 100gm/week or moderately potent corticosteroid should be applied if systemic absorption is to be avoided.

Usage in Pregnancy:

These are pregnancy category C drugs. Hence, caution is to be exercised when used in pregnancy. It is not known whether they are secreted in breast milk and they are never to be used on the breasts before breast feeding.

Halobetasol is a superpotent synthetic topical corticosteroid and has marked anti-inflammatory and anti-pruritic effects. Its chemical structure is: 21-chloro-6 alpha,9-difluro-11 beta,17-dihydroxy-16 beta-methylpregna-1,4-diene-3,20-dione 17 propionate. Treatment beyond two weeks is not recommended, and total dosage should not exceed 50mg/week because of the potential to suppress the HPA axis. Use in children <12years is not recommended. It is contraindicated in patients with sensitivity to the test medications.

Use in Lichen planus:

Although topical and intralesional steroids are the first line treatment, their use has been based on anecdotal reports rather than controlled clinical trials[49].

Potent topical steroids (Fluocinonide 0.05%, Clobetasol propionate 0.05%) form the mainstay of therapy of localised lichen planus lesions. These are applied twice daily for two weeks. In large areas of involvement they can be used in a diluted form (1:4 in white soft paraffin)[50].

In treatment of oral lesions with triamcinolone, use of occlusive materials like Orobase provides protection and sustained tissue contact with the glucocorticoid as well as alleviates the discomfort of oral lesions. 0.1%fluocinolone acetonide and 0.05% Clobetasol propionate in Orobase showed good results. Application is 4–6 times per day[51]. Corticosteroid lozenges, betamethasone mouth washes 0.5mg 3-4 times daily[52] are beneficial.

Vulvovaginal lichen planus can be treated with vaginal hydrocortisone suppositories[53]. Sialistic prosthetic devices have been used to increase the delivery of topical corticosteroids to mucosal surfaces like vagina and buccal mucosa[54].

Hypertrophic lesions and palmoplantar lesions benefit from the use of potent topical corticosteroids under occlusion.

Rubbing a potent topical corticosteroid on the nail folds maybe helpful in the active stage of the disease[55]. Topical anaesthetics maybe combined with topical corticosteroids for relief of pain in mucosal lesions.

Topical Calcineurin inhibitors:

Topical calcineurin inhibitors like Tacrolimus, Pimecrolimus, Cyclosporine have been used to treat lichen planus. These are non-steroidal agents that act through immunological pathways to modify the immune and inflammatory responses in skin.

Tacrolimus:

Tacrolimus is a macrolactam class of cytokine inhibitor and is anti-Inflammatory[56].

It was first isolated from a soil fungus Streptomyces tsukubaensis near Tsukuba, Japan. It was known earlier as FK506, its experimental name. Its new name is derived from **T**sukuba, the location of its discovery, m**acrol**ide, its chemical class, and **im**m**u**ne **s**uppressant, its primary activity in humans[57].

Mechanism of action: Tacrolimus is an inhibitor of the phosphatase, calcineurin .

T-lymphocyte activation occurs through the following steps:

1) Interaction of co-stimulatory ligands on antigen-presenting cells with T-cell receptors
2) Increase in levels of free calcium within the cell
3) Binding of calcium to calmodulin,which in turn activates calcineurin [Calcium/Calmodulin dependant serine/threonine phosphatase]
4) Dephosphorylation of cytoplasmic subunit of the nuclear factor of activated T cells[NFAT] by calcineurin
5) Translocation of the dephosphorylated subunit to the nucleus, formation of a complex and transcription of cytokines like IL-2, IL-3,IL-4,IL-12,TNF-alpha,IFN-gamma[58]

Tacrolimus binds to the FK-506 binding protein [FKBP], forming complexes that inhibit calcineurin , thus preventing its dephosphorylation activity and production of cytokines necessary for T cell activation.

Effects include

1) inhibition of T cell proliferation

2) inhibition of production of cytokines IL-2,IL-3,IL-4,IL-12,TNF-alpha, IFN-gamma
3) inhibition of mast cell adhesion
4) inhibition of release of mediators from mast cells and basophils
5) down regulation of the expression of IL-8 receptor and FcεRI on Langerhans cells[59]
6) Acts on keratinocytes to increase stem cell factor release ,causing proliferation of melanocytes and melanoblasts[60] in vitiligo
7) Also influences nerve fiber function by binding to a receptor on small unmyelinated sensory nerve fibres, the TRPV1[61] [Transient Receptor Potential cation channel subfamily V member 1, the capsaicin receptor] Activation of this receptor results in transmission of burning pain and itch. This explains the initial burning and pruritus on application. Continuous stimulation of the receptor causes it to be finally desensitised.

Tacrolimus is effective even when applied topically by affecting local immunosupression at areas of application. Tacrolimus is 10-100 times more potent than cyclosporine in inhibiting T cell activation and its ability to penetrate the skin is greater. Moreover, topical formulation delivers the active ingredient directly to the inflamed sites in the skin while minimising the systemic exposure of tacrolimus[52]. Tacrolimus has

been found to cause significantly less atrophy than topical corticosteroids[54] as it does not alter the collagen synthesis even under occlusion.

Formulations:

Both 0.03% and 0.1% are available.0.1% has been shown to be more effective in treating lesions of erosive oral lichen planus[63],erosive lichen planus of the sole[64] ,vulvovaginal lichen planus[65] as damaged skin has sevenfold higher rate of absorption of tacrolimus. There has been a case report on the successful use of topical tacrolimus in cutaneous lichen planus[66] and also in nail lichen planus[67].

Adverse effects:

The major adverse effect is local irritation mainly burning and stinging at the site of application. Allergic contact dermatitis, rosacea like granulomatous reaction, increased incidence of skin infections have also been reported. There is theoretical risk of increased malignancy in patients treated with tacrolimus.

Contraindications include pregnancy, infected lesions and exposure to sunlight. Vaccinations cannot be given during treatment and for 28 days after that. Safety has not been evaluated in children younger than 2 years and in nursing mothers

Topical cyclosporine 5 ml of 100 mg/ml solution 3 times a day can be used as mouthwash [swish for 5 minutes and spit] or manually by local massage[68].

Topical Retinoids:

Topical retinoids like Retinaldehyde[70], Isotretinoin gel (0.1%)[69], tazarotene[71], etretinate[72] have been tried in treatment of oral lichen planus.

Others:

Topical calcipotriol is of limited use in cutaneous lichen planus[73] .Topical Aloe Vera gel[74], Imiquimod 5% cream[75], topical tetracycline[76] have also been tried in oral lichen planus.

Intralesional steroids:

Intralesional triamcinolone acetonide (5 to 10 mg/dL) is effective in treating oral and cutaneous lichen planus. For hypertrophic lichen planus, 10-20 mg/dL may be required once in 3-4 weeks. It may also be used for lichen planus of the nail with injection every 4 weeks. Regression occurs within 3-4 months. Side-effects include atrophy, localised hypopigmentation or depigmentation and telangectasia

SYSTEMIC THERAPY:

Systemic steroids:

***Indications*:**

1) generalised eruptive lichen planus
2) progressive nail lichen planus
3) active stage of follicular lichen planus of scalp causing alopecia
4) erosive oral or genital lichen planus

Usually, prednisolone in the dose of 0.5-1 mg/kg body weight in a gradually tapering dose for 6 weeks is helpful. Symptoms are alleviated and patients experiencing a flare have marked response. However, relapse may occur with quick tapering of therapy. Long term continuation is contraindicated due to high risk of complications.

Adrenocorticotrophic hormone (ACTH])or tetracosactin may also be used[50]

***Pulse therapy*:**

Synder et al[77] described use of pulse therapy with methylprednisolone 1 g daily for 3 days each month for 3 months.

Systemic Retinoids:

Their anti-inflammatory property has been used in treatment of lichen planus. Acitretin, used in dosages of 30 mg/day for 8 weeks

showed marked improvement[78].Oral tretinoin used at 10-30 mg/day[79], low dose etretinate[80] 10-20 mg/day for 4-6 months have also shown improvement. Isotretinoin in the dose of 20-40 mg/day has also been tried[81].

Immunosuppressive agents:

1) Systemic cyclosporine has been tried for recalcitrant lichen planus, severe oral erosive lichen planus in the dose of 1-6 mg/ kg/ day[82].It is also a therapeutic option for severe nail lichen planus[55]. Side effects like renal toxicity, hypertension and relapse after discontinuation of cyclosporine limit its use to only severe cases.
2) Azathioprine[83] is useful in recalcitrant, generalised cutaneous lichen planus.
3) Methotrexate[84], Mycophenolate moefitil[85], Cyclophosphamide[86] have also been tried in refractory cases

Others:

i) Dapsone in doses of 100-200 mg / day [87] has been found effective in patients with cutaneous and oral disease.
ii) Antimalarials like hydroxychloroquine at doses of 200-400 mg/day is helpful in actinic and oral lichen planus[88].
iii) Thalidomide can be tried in recalcitrant cases[89], treatment of lichen planopilaris of scalp[90].

iv) Metronidazole can be tried in cutaneous and severe oral lichen planus[91].

v) Antifungals: Griseofulvin[92] has been found to be effective in treatment of lichen planus. Itraconazole[93] has also been tried.

vi) Combination therapy with tetracycline or doxycycline and nicotinamide has been reported as useful in treatment of lichen planus pemphigoides[94].

vii) Low molecular weight heparin in doses of 3 mg weekly subcutaneous injections has been found to be effective in cutaneous and reticulated oral lesions[95].

viii) Interferon α2b has been administered for treatment of generalised lichen planus though this response modifier has also been implicated in the development or exacerbation of lichen planus[96].

ix) Others like phenytoin[97],sulfasalazine[98] ,basiliximab[99], efalizumab[100],alefacept[101] have also been tried in the treatment of lichen planus.

Photochemotherapy :

i) PUVA can be used alone or in combination with steroids to hasten the response[102] in generalised cutaneous lichen planus. RePUVA can also be tried though it is found to produce hyperpigmentation[103].

ii) UVA_1 phototherapy may help in protracted lichen planus[104].

iii) NB UVB is useful in treatment of widespread cutaneous lichen planus[105].

Lasers:

i) Excimer laser was found to be very effective in one study for the treatment of erosive oral lichen planus[106].

ii) Nd YAG, Carbon dioxide lasers have also been used to treat oral lichen planus[107].

Photodynamic therapy:

Resistant and recurrent cases of oral lichen planus have been treated with photodynamic therapy mediated methylene blue(MB-PDT)[108].

Extracorporeal photopheresis:

It has been found to be effective in treatment of erosive oral lichen planus[109] but concomitant topical treatment is required.

Follow up:

Lichen planus runs a chronic course , over months to years. Relapse occurs in 15-20% of cases[1].Generalised eruptive lichen planus and erosive lichen planus are particularly prone to relapse and chronicity.

Patients with variants at risk of malignant transformation should be regularly followed up and repetitive biopsies may be needed to rule out malignancy.

Monitoring of therapeutic response can be done by certain biochemical parameters. Response in oral lichen planus can be monitored by salivary analysis of NFκB dependant cytokines (TNF-alpha, IL- 12, IL-6, IL-8) but its value is signicantly reduced by treatment with dexamethasone [110].Estimation of serum ACE activity , though non-specific, may be a good parameter for assessing the therapeutic response[111].

AIM OF THE STUDY

To compare the efficacy of topical halobetasol and topical tacrolimus in the treatment of localised cutaneous lichen planus lesions.

Agents compared:

1) 0.05% Halobetasol propionate ointment
2) 0.1% Tacrolimus ointment

MATERIALS AND METHODS

Study design: prospective, randomised, open label clinical trial.

Study subjects: Sixty subjects with cutaneous lichen planus.

Study duration: August 2008 to August 2010.

Study setting: Out-patient department of the Department of Dermatology, Government General Hospital, Chennai.

Ethical committee: Approved

Inclusion Criteria:

1) Subjects of either sex with biopsy confirmed symptomatic localised (< 10% of body surface area) lichen planus lesions.
2) Subjects who have not been on any form of therapy for atleast a month prior to their enrolment.

Exclusion Criteria:

1) Lichen planus with facial/ mucosal involvement.
2) Use of drugs known to produce lichenoid reaction.
3) Pregnant/ lactating women.
4) Children < 12 years of age.
5) Subjects with prior history of hypersensitivity to any of the

components of the test medications.

Treatment protocol and Methodology:

Subjects attending the out-patient department of the Department of Dermatology, Government General Hospital, Chennai who met the above mentioned inclusion criteria were offered to participate in the study. Those who elected to participate in the study signed an informed consent.

At baseline:

Clinical profile:

Demographic data such as age, sex, occupation, marital status and were taken.

Severity of itching, duration and progression of lesions, family history of lichen planus, past and present history of topical and systemic treatment for lichen planus, h/o intake of drugs known to induce a lichenoid reaction, h/o contact with photodevelopers, h/o recent vaccination for hepatitis B were noted.

History of diabetes, hypertension, jaundice, thyroid disorders,radiation therapy to the site of involvement, recent mental stress,anxiety,

alopecia areata, vitiligo, morphea, dermatomyositis, SLE, pemphigus were asked for.

Patients were subjected to general and systemic examination. Blood pressure was noted. Thorough dermatological examination was done and other dermatological lesions, site of involvement of lichen planus, morphology of lesions, number of lesions, koebners phenomenon were recorded. Blood group was noted.

Blood glucose, complete blood count, hepatic and renal chemistry, VDRL, rapid tests for HIV were done at baseline. Photography was taken at baseline. Diagnosis was arrived based on clinical grounds and biopsy.

Study:

- Patients were randomly allocated into the 2 groups.
- The study was divided into 2 phases.

  Phase 1 consisted of topical treatment for 2 weeks.

  Phase 2 was a two month follow-up period without any therapy

<u>Phase 1</u>:

Group 1:

Patients in this group received 0.05% halobetasol propionate ointment. The patients were advised to apply the ointment only over the lesions twice daily for a period of 2 weeks or until the lesions cleared, whichever was earlier & to avoid using the medication over ulcerated areas. Patients were instructed to refrain from using other topical or systemic medication for lichen planus for the above period. They were asked to come at weekly intervals for 2 weeks for assessment. The patients were asked to return all unused medication at each visit and the quantity of returned medication was used to assess patient compliance. Patient Visual Analogue Scale for pruritus [VAS consisted of a horizontal line marked 0(= no itching) to 10(= more severe itching)] and Clinician VAS for thickness [0= flat to 10= highly raised] were marked & photographs were taken at each visit. They were instructed about the side effects of therapy like hypopigmentation, atrophy, impaired wound healing, folliculitis, increased infections at the application site and to report them if any. Signs of the adverse effects like hypopigmentation, atrophy, purpura, telangectasia, folliculitis, miliaria, acneiform eruptions were also looked for at each visit.

Group 2:

Patients in this group received 0.1% tacrolimus ointment & were advised to apply the ointment only over the lesions twice daily for a period of 2 weeks or until the lesions cleared, whichever was earlier. They were also asked to refrain from using other topical or systemic medication for lichen planus for the above period. The patients were asked to return all unused medication at each visit and the quantity of returned medication was used to assess patient compliance. Assessment was done at weekly intervals. Patient Visual Analogue Scale for pruritus and Clinician VAS for thickness were marked and photographs were taken at each visit. They were instructed about the side effects of therapy like burning, stinging & increased infections at the site of application and were asked to report them, if any, at each visit. Signs of the adverse effects were also looked for at each visit.

Evaluation of response:

The symptomatology score was obtained using the patient's Visual Analogue Scale & the signs were assessed based on the clinician's VAS score for thickness at each visit and a decrease, an increase or no change in the score meant response, worsening or persistence of the condition respectively.

Improvement ratio was calculated as follows.

$$\text{Improvement ratio} = \text{Pre-treatment total score} - \frac{\text{post-treatment total score}}{\text{Post- treatment total score}} * 100$$

Based on the improvement ratio, physician's clinical evaluation of the change in disease status was made according to the following criteria:

1) *cleared* : improvement ratio = 100 (except for post-inflammatory hyperpigmentation)
2) *marked improvement* : improvement ratio = 75 to <100
3) *moderate improvement* : improvement ratio = 50 to < 75
4) *slight improvement* : improvement ratio = < 50
5) *no change* = no detectable improvement from pre-treatment evaluation
6) *Exacerbation* = flare of sites monitored

Phase 2:

Follow-up:

Follow-up of the two groups was done at 4 weeks and 8 weeks after the cessation of therapy. Patients were asked not to use any concurrent medication for the lesions & the following were noted.

i) occurrence of new lesions ii) relapse of lesions at the same site iii) exacerbation of the existing lesions iv) no change in the existing lesions.

Statistical Analysis:

1. In each study group, mean values for pruritus and thickness scores were calculated and compared using Non-parametric repeated measures ANOVA test (Friedman test).
2. To look for significant association between the response and the sex, age, duration, site of involvement and the blood group, Fisher's Exact test was used.
3. A p value of < 0.05 was considered statistically significant.

OBSERVATIONS

The following observations were made in the present study.

Among the 60 patients under study, 31 were males and 29 were females. They were in the age group ranging from 13 years to 69 years with mean age of 35.4 years. The duration of lichen planus ranged from 2 weeks to 2 years with mean duration of 5.5 months. Family history of lichen planus was positive in 6.7% of patients, all had onset < 20 years of age. History of previous topical application was present in 15% of patients. The time interval between the last and the present therapy ranged from 1 to 6 months. None of them had had systemic treatment.

1) Sex Distribution

Sex	***No of patients***	***Percentage***
Male	31	52%
Female	29	48%

2) Age distribution

Age	***Males (n=31)***	***%***	***Females (n=29)***	***%***
10-20 Years	6	19	5	17
20-30 Years	**7**	**23**	**6**	**21**
30-40 Years	**8**	**26**	**8**	**27**
40-50 Years	5	16	4	14
50-60 Years	4	13	2	7
> 60 Years	1	3	4	14

3) Duration of lesions:

Duration	***Males n=31***	***Females n=29***
< 1 month	6	9
1 month – 6 months	14	16
6 months – 12 months	7	2
> 12 months	4	2

4) Blood group distribution

O was the predominant blood group followed by A in this study.

Blood Group	***Males n=31***	***%***	***Females n=29***	***%***
O+ve	**11**	**35**	**10**	**35**
O-ve	**3**	**10**	**2**	**7**
A+ve	8	26	9	31
A-ve	0	0	3	10
B+ve	6	19	2	7
B-ve	1	3	0	0
AB+ve	2	7	3	10
AB-ve	0	0	0	0

5) Type of lesions

The majority (62%) presented with classical lichen planus; pigmentation was seen in all patients and a large proportion had the typical features of violaceous colouring, scaling and Wickham's striae. All patients had pruritus.

Type Of Lesion	***Males n=31***	***%***	***Females n=29***	***%***
Classical	**17**	**55**	**20**	**69**
Hypertrophic	9	29	6	21
Linear	3	10	3	10
LP of the palms and soles	2	6	0	0

6) Site of involvement

Lower limb (53.5%) was the most common site of involvement.

Site	***Males n=31***	***%***	***Females n=29***	***%***
Upper Limbs	11	35	11	38
Trunk	1	3	3	10
Lower Limbs	**17**	**55**	**15**	**52**
Palms and Soles	2	7	0	0

7) Autoimmune disorders associated

Other autoimmune disorders associated were vitiligo vulgaris, diabetes mellitus and alopecia areata.

Diseases	***Male n=31***	***Female n=29***
Vitiligo Vulgaris	3	1
Diabetes Mellitus	2	5
Alopecia Areata	1	0

8)Demographics

The baseline demographics of the two study groups were comparable with respect to sex distribution, mean age, mean duration of lesions, type of lesions, site of involvement and blood group.

Variables	***Group 1 Halobetasol***	***Group 2 Tacrolimus***
No of patients	30	30
Gender (M/F)	16/14	15/15
Mean duration of lesions	166 days	163 days
Mean Age	34.5 years	36.2 years
Type of lesions		
Classical	18	19
Hypertrophic	9	6
Linear	2	4
LP of palms/soles	1	1

Site of involvement		
Upper limb	10	12
Lower limb	17	15
Trunk	2	2
Palms and Soles	1	1
Blood group		
O+VE	10	11
O-VE	3	2
A+VE	8	9
A-VE	2	1
B+VE	3	5
B-VE	1	0
AB+VE	3	2
AB-VE	0	0

THERAPEUTIC RESPONSE:

Pruritus-Response:

The patient Visual Analogue Scale scores for pruritus

1) in the halobetasol group in weeks 1 and 2 dropped from a mean of 6.13 at baseline to 3.6 at day 7 and 1.5 at day 14 which were both statistically significant($p<0.01$).

2) in the tacrolimus group, the mean had dropped from 6.13 to 4.63 at day 7(statistically significant, $p<0.01$) and 2.63 at day 14(statistically significant, $p<0.01$)

The difference between the mean scores of pruritus between the two groups had a p value of 0.018(statistically significant) at the end of 2 weeks.

Patient VAS score at baseline (0 weeks), 1 & 2 weeks with halobetasol

Pruritus	***0 Week***	***1 Week***	***2 Weeks***
Mean	6.13	3.6	1.5
p value		< 0.01	<0.01

Patient VAS score at baseline (0 weeks), 1 & 2 weeks with tacrolimus

Pruritus	***0 Week***	***1 Week***	***2 Weeks***
Mean	6.13	4.63	2.63
p value		< 0.01	<0.01

Treatment differences from VAS assessments between Halobetasol and Tacrolimus at 2 weeks

Pruritus	***Halobetasol***	***Tacrolimus***	***p value***
Mean	1.5	2.63	0.018

Thickness – Response:

The physician Visual Analogue Scale scores for thickness

1) in the halobetasol group dropped from a mean of 6.4 at baseline to 4.03 at day 7 and 2.33 at day 14 which were both statistically significant.(p value <0.01)
2) In the tacrolimus group, the mean dropped from 6.36 at baseline to 5.43 at day 7(p value >0.05,not statistically significant) and 4.26 at day 14(p value < 0.01,statistically significant)

The difference between the two groups in the mean scores of thickness had a p value of 0.03 at the end of 1 week and 0.0074 at the end of two weeks which were both statistically significant.

Physician VAS score at baseline (0 weeks), 1 & 2 weeks with halobetasol

Thickness	***0 Week***	***1 Week***	***2 Weeks***
Mean	6.4	4.03	2.33
p		< 0.01	<0.01

Physician VAS score at baseline (0 weeks), 1 & 2 weeks with tacrolimus

Thickness	***0 Week***	***1 Week***	***2 Weeks***
Mean	6.36	5.43	4.26
p		>0.05	<0.01

Treatment differences obtained from VAS assessments between Halobetasol and Tacrolimus at 1 week

Thickness	***Halobetasol***	***Tacrolimus***	***p Value***
Mean	4.03	5.43	0.03

Treatment differences obtained from VAS assessments between Halobetasol and Tacrolimus at 2 weeks

Thickness	***Halobetasol***	***Tacrolimus***	***p Value***
Mean	2.33	4.2	0.0074

7th day of clinical assessment

1) In the halobetasol group, 1 patient cleared, 7 showed marked improvement, 8 showed slight improvement and 2 had no change in lesions. Majority (40%) were in the moderate improvement category.
2) In the tacrolimus group, no patients cleared or showed marked improvement, majority of patients (46.6%) were in the slight improvement category, 7 had moderate improvement and 9 had no change in the lesions.

14th day of clinical assessment

1) In the halobetasol group, all patients showed improvement of whom 10 cleared, 8 had marked improvement, 8 had moderate improvement and 4 showed slight improvement.
2) In the tacrolimus group, 2 cleared, 11 had slight improvement, 5 had marked & 5 had moderate improvement, 7 had no change. Exacerbation was not seen in any patient.

The difference between the two groups in clearance rates showed a statistically significant difference at the end of 2 weeks with a p value

of 0.021.

Clinician assessment of change in disease status

	DAY 7		***DAY 14***	
	Halobetasol	***Tacrolimus***	***Halobetasol***	***Tacrolimus***
Cleared	1(3.3%)	-	10(33.3%)	2(6.67%)
Marked Improvement	7(23.3%)	-	8(26.7%)	5(16.6%)
Moderate Improvement	12(40%)	7(23.3%)	8(26.7%)	5(16.6%)
Slight Improvement	8(26.6%)	14(46.6%)	4(13.3%)	11(36.7%)
No Change	2(6.7%)	9(30%)	-	7(23.3%)
Exacerbation	-	-	-	-

Follow-up:

1) At week 4 of follow-up, 36.6% of patients in the halobetasol group and 43.3% of patients in the tacrolimus group developed new lesions. Relapse of lesions were found in 5(16.6%) of halobetasol and 1 (3.33%) of tacrolimus group. No change in existing lesions was found in 23.3% of halobetasol and 33.3 % of tacrolimus group.

2) At week 8 of follow-up, number of new lesions increased in both the groups with 46.6% of patients in the halobetasol group and 53.3% of patients in the tacrolimus group having new lesions, with no significant difference between the two. Significant difference was seen in the relapse of lesions, with more people in the halobetasol group experiencing relapse compared to the tacrolimus group(p=0.04 by Fisher's exact test).

Follow-up period

	Halobetasol		***Tacrolimus***	
	Week 4	***Week 8***	***Week 4***	***Week 8***
New Lesions	11(36.6%)	14(46.6%)	13(43.3%)	16(53.3%)
Relapse	5(16.6%)	9(30%)	1(3.33%)	2(6.67%)
Remission	10(33.3%)	3(10%)	7(23.3%)	4(13.3%)
No Change In Existing Lesions	7(23.3%)	6(20%)	10(33.3%)	10(33.3%)

Adverse effects:

No serious adverse effects were noted. About 40% of patients in the tacrolimus group experienced mild burning sensation, more on the first week of treatment. This subsided spontaneously and no patient discontinued treatment.

In the halobetasol group, no significant side effect was noted. The most common adverse effect noted was the hypopigmented halo around the lesions, which was seen in 36% of patients.

Assessment of response based on sex

With respect to sex, no significant difference in treatment response was seen in both the groups.

	Halobetasol		***Tacrolimus***	
	Male	***Female***	***Male***	***Female***
Cleared	4	6	1	1
Marked Improvement	4	4	2	3

Assessment of response based on age

With respect to age, no significant difference was seen in the halobetasol group with respect to rate of clearance. In the tacrolimus group, clearance and marked improvement was seen in the 20-40 years age group.

	H	***T***	***H***	***T***	***H***	***T***	***H***	***T***	***H***	***T***	***H***	***T***
	11-20 yrs		***21-30 yrs***		***31-40 yrs***		***41-50 yrs***		***51-60 yrs***		***>60 yrs***	
Cleared	2	-	2	1	3	1	2	-	-	-	1	-
Marked Improvement	3	-	2	2	1	3	1	-	-	-	1	-

Assessment of response based on site of involvement

With respect to the site of involvement, there was no significant difference in the rate of clearance between the exposed and non-exposed ($p = 0.3985$) areas in the halobetasol group whereas in the tacrolimus group, good response was observed in lesions over the exposed areas ($p = 0.02$ by Fisher's exact test).

	H	***T***	***H***	***T***
	Exposed sites		***Unexposed sites***	
Cleared	5	2	5	-
Marked Improvement	6	5	2	-

<u>Assessment of response based on blood group</u>

With respect to the blood group, all patients in blood group O responded to tacrolimus, and all patients who cleared were in the O group. In the halobetasol group, no significant difference in clearance was seen between O and A groups.

	H	***T***	***H***	***T***	***H***	***T***	***H***	***T***
	O group		***A group***		***B group***		***AB group***	
Cleared	4	2	6	-	-	-	-	-
Marked Improvement	4	3	1	1	1	-	2	1

Assessment of response based on duration

With respect to the duration of lesions, early lesions showed a better response with tacrolimus. Both lesions which cleared belonged to the <1 month category.

	H	***T***	***H***	***T***	***H***	***T***	***H***	***T***
	<1 month		***>1month-6months***		***>6 months - 1year***		***>1 year***	
Cleared	4	2	4	-	1	-	1	-
Marked Improvement	3	3	3	2	2	-	-	-

DISCUSSION

In our study, we found males and females to be equally affected which was consistent with the study done by Bhattacharya et al[19]

Increased prevalence of lichen planus was found in patients aged between 20 and 40 years of age which is lower than that described[1] but consistent with the study by Bhattacharya et al[19]

Family history of lichen planus was found in 6.7% of patients in our study, all of whom had onset of lesions within 20 years of age. Hereditary factor in the causation of lichen planus has been documented.

The association of lichen planus with blood group A has been described[20]. In our study, we found an increased incidence among patients with blood group O followed by blood group A.

Studies reveal the predominance of classical type among patients of lichen planus[19,112]. Our study was consistent with them.

Though topical steroids are the 1st line treatment and are commonly used in lichen planus, very few clinical trials on the treatment of cutaneous lichen planus with topical steroids are available and no convincing evidence of their efficacy is seen in literature.

Moreover, though a case of cutaneous lichen planus reported by Fortina et al[66] showed a dramatic response to tacrolimus, stressing that topical tacrolimus may be an effective therapy for cutaneous lichen planus, to the best of our knowledge, there is no clinical trial dedicated to the treatment of cutaneous lichen planus with tacrolimus, especially from India and no evidence of its efficacy.

Large and randomised trials are difficult to perform in lichen planus as no standardised methods exist for evaluation of the severity of the disease, no consensual criteria of improvement or cure and variable course of the disease according to the clinical form or individual.

In our study,

Group 1 [Halobetasol group]

Halobetasol caused a statistically significant improvement in pruritus and reduction in thickness within 1 week of commencement of therapy. The clinician assessments at the end of 1 week showed marked improvement and clearance of lesions in >25% of patients. At the end of 2 weeks, marked improvement and clearance of lesions was seen in 60% of patients. Within 8 weeks of cessation of therapy, out of 30 patients, 9 (30%) suffered a relapse.

Though adverse effects are expected to occur with the use of superpotent steroids, due to the shorter period of time used, there were no significant side effects associated with the use of halobetasol in our study except for hypopigmentation around the lesions. There was no significant difference in the rate of response with respect to age, sex or site of lesions. All patients showed improvement.

Group 2 [Tacrolimus group]

Patients in this group experienced a significant reduction in pruritus & it was statistically significant at 1 week of therapy. The clinician assessments at the end of the first week showed that none of the patients cleared or showed marked improvement .The reduction in thickness was also not significant at the end of 1 week. At the end of 2 weeks, 6.7% of patients cleared and 16.6% showed marked improvement. Although topical tacrolimus is effective in controlling disease, it rarely seems to result in complete remission within 2 weeks, probably due to slow onset of action.

There was no significant difference in the rate of response with respect to sex. Patients with blood group O and lesions with a shorter duration responded better to tacrolimus than other blood groups and those with long-standing lesions, it was however not statistically significant.

Local irritation in the form of burning was the most common adverse effect noted that subsided with continued treatment which is probably due to its action on nerve fibre function[61].

Those patients with lesions on the exposed sites responded better than those on unexposed sites (p value<0.05). Silverberg et al[113] suggested that the combination of tacrolimus ointment and UV light might be superior to that of tacrolimus ointment alone, but that UV light is not necessary for the beneficial effect of tacrolimus ointment. This probably could explain the better response seen in the exposed parts. In our study, treatment of localised cutaneous lichen planus over the exposed parts with tacrolimus is promising. However, this study is the first of its kind and more robust data need to be obtained in large double-blind controlled studies.

In the follow up period, at the end of 8 weeks, out of 30 patients, 2(6.7%) patients suffered a relapse, which was lower than the halobetasol group.

In comparison, there is a statistically significant difference in the symptomatic improvement and clearance rates with halobetasol at the end of 2 weeks of therapy compared to tacrolimus (p value <0.05).The greater reduction in thickness with halobetasol could be due to its anti-

proliferative effect[47] in addition to its anti-inflammatory and immunosuppressive effect. Relapse rates were lower with tacrolimus group compared to the halobetasol group (p value< 0.05).

Thus, our study suggests that though halobetasol is known to be very effective, tacrolimus might have a role in the management of early lesions and as maintenance regimen for localised cutaneous lichen planus. The major limitation of our study is the small sample size. Hence, larger trials with long term follow-up are needed to prove the efficacy, safety and stability of response with topical tacrolimus in the treatment of cutaneous lichen planus.

CONCLUSION

- In this study, males and females were found to be equally affected with lichen planus.
- Increased prevalence was noted in the age group of 20-40 years.
- The predominant blood group in this study was blood group O.
- The predominant type of lichen planus was the classical type.

- **After 2 weeks of study period, topical *halobetasol* caused a significant reduction in symptoms (p value = 0.018) and clearance rates (p value=0.021) compared to tacrolimus in localised cutaneous lichen planus.**

- **After 8 weeks of follow-up, topical *tacrolimus* resulted in lower relapse rates compared to halobetasol (p value = 0.04).**

- **In the halobetasol group, there was no change in rate of response with respect to site of involvement, blood group or duration of lesions.**

- **In the tacrolimus group,**
  - **better response was seen over the exposed parts compared to the non-exposed parts (p value = 0.02)**
  - **Patients with blood group O and shorter duration of lesions responded better compared to other blood groups and long-standing lesions. However, the differences were not statistically significant.**

- **This is the first study comparing topical halobetasol and topical tacrolimus head-to-head. Prospective randomized trials with more subjects are needed before any treatment recommendations can be made based on the conclusions of our study.**

Treatment with 0.05% Halobetasol Ointment

BEFORE TREATMENT

AFTER TREATMENT

BEFORE TREATMENT

AFTER TREATMENT

BEFORE TREATMENT

AFTER TREATMENT

BEFORE TREATMENT

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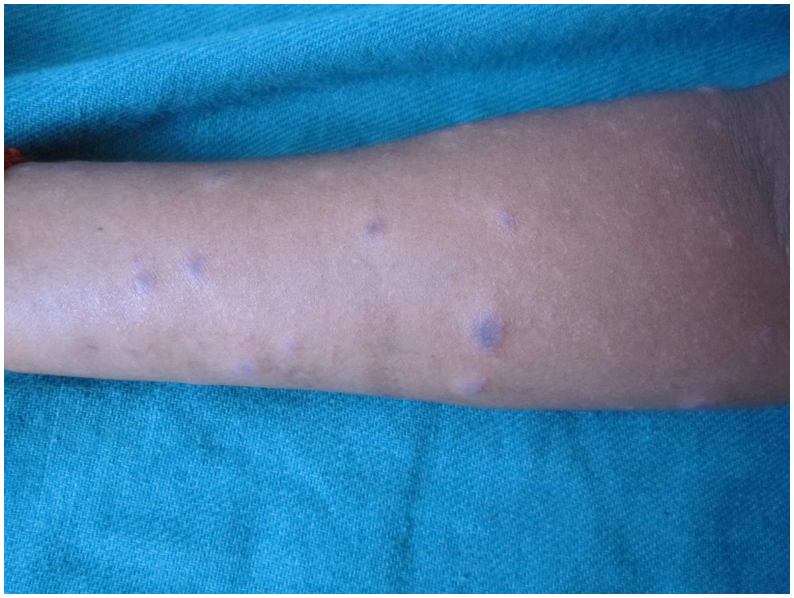
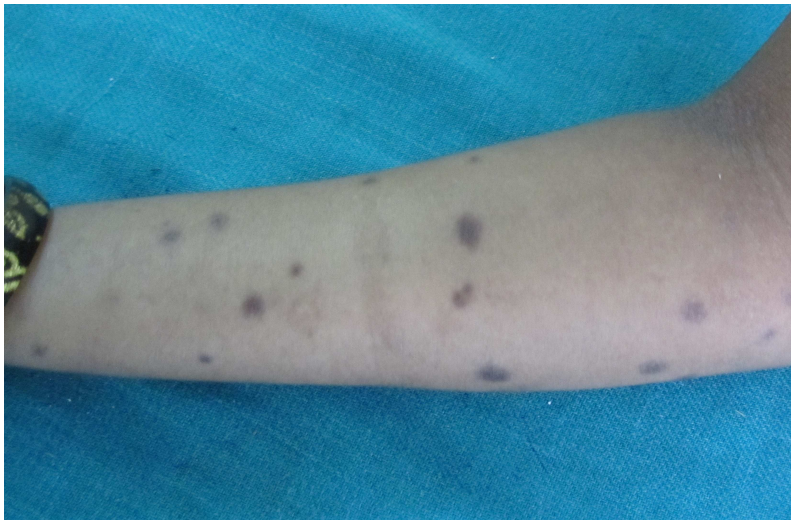
BEFORE TREATMENT



AFTER TREATMENT

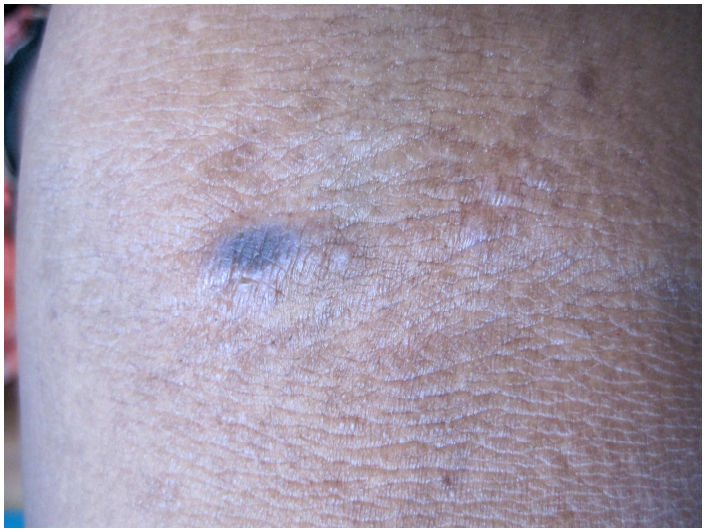


Treatment with 0.1% Tacrolimus Ointment

BEFORE TREATMENT

AFTER TREATMENT

BEFORE TREATMENT



AFTER TREATMENT

BEFORE TREATMENT

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PROFORMA

Name: Age: Sex:

OP no: Blood group:

Occupation:

Address:

Presenting complaints:

Duration:

Onset: sudden / insidious

Progression:

H/O itching :

H/O photosensitivity: yes / no

H/O previous systemic or topical treatment for LP:

H/O drug intake for DM/ HT/ TB/Epilepsy:

H/O genital lesions:

H/O burning sensation on taking food:

H/O excessive hair fall:

H/O bullous lesions:

H/O jaundice:

H/O loss of weight/loss of appetite:

H/O contact with photodevelopers:

H/O recent hepatitis B vaccination:

H/O dental procedures:

H/O X-ray/ radiation exposure :

H/O chronic bladder infections:

H/O amoebiasis:

H/O suggestive of vitiligo/ morphea/

myasthenia gravis/SLE/dermatomyositis:

H/O recent mental stress/ anxiety/ depression:

Past history:

H/O similar episodes in the past & treatment taken:

H/O DM/ HT/ TB/ Malaria/ Epilepsy:

Personal history:

Married / Unmarried

No of children:

Smoker / Alcoholic

Tobacco usage:

H/O exposure to STD:

Family history:

General examination:

Anemia / Cyanosis / Jaundice / Clubbing / Pedal edema /

Lymphadenopathy

Pulse:	CVS:	RS:
BP:	P/A:	CNS:

Dermatological examination:

Site of involvement:

Distribution:

No of lesions:

Morphological type:

Koebnerisation:

Exposed / Unexposed site:

Mucous membrane (oral/ genital):

Palms and soles:

Nails:

Associated skin lesions:

Investigations:

Blood:

1) Complete Blood Count
2) Blood sugar
3) Liver Function Tests
4) Renal Function Tests
5) Blood grouping
6) VDRL
7) HIV

Urine routine:

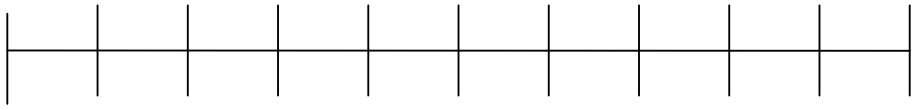
Skin Biopsy:

Treatment:

<u>Evaluation of response</u>:

0 WEEK:

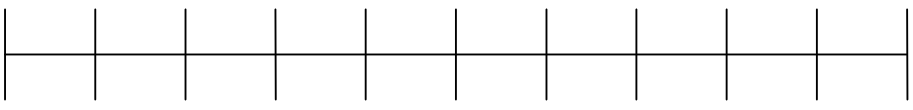
1) Patient VAS for pruritus:



0 1 2 3 4 5 6 7 8 9 10

No itch severe itch

2) Physician VAS for thickness:

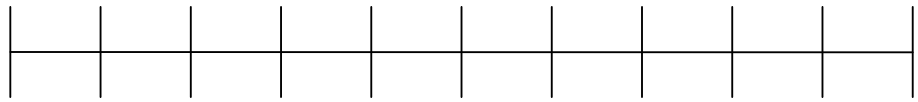


0 1 2 3 4 5 6 7 8 9 10

Flat highly raised

WEEK 1:

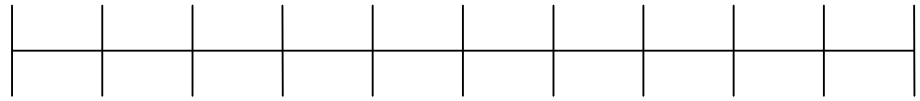
1) Patient VAS for pruritus:



0 1 2 3 4 5 6 7 8 9 10

No itch severe itch

2) Physician VAS for thickness:



0 1 2 3 4 5 6 7 8 9 10

Flat highly raised

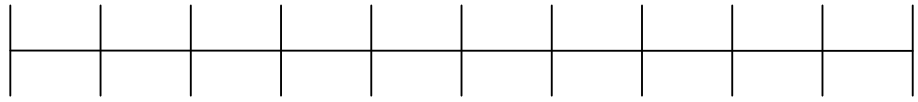
3) Adverse effects:

4) No of lesions:

5) New lesions:

WEEK 2:

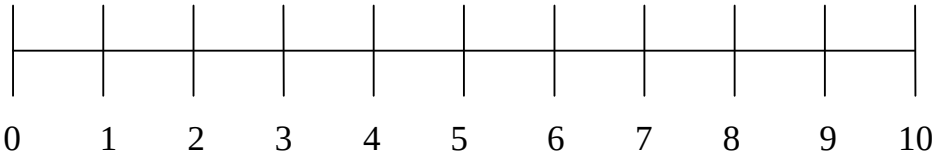
1) Patient VAS for pruritus:



0 1 2 3 4 5 6 7 8 9 10

No itch severe itch

2) Physician VAS for thickness:



Flat highly raised

3) Adverse effects:

4) No of lesions:

5) New lesions:

FOLLOW –UP:

	Week 4	Week 8
New lesions		
Relapse		
Remission		
No change in lesions		
Itching		

RESPONSE:

Cleared	**Mild Improvement**	**Moderate Improvement**	**Slight Improvement**	**No response**	**Exacerbation**

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE,CHENNAI-600 003.

Telephone : 25363970

Fax :044 – 253-5115
:044 25363970

L.Dis.No. 14597/ M E 5/ EthicsDean/MMC/2009 Dated .09.2009

Title of the work : "Comparitive study of 0.05% Halobetasol propionate ointment & 0.1% Tacrolimus ointment in treatment of Lichen planus

Principal Investigator : Dr. Vidhya Ravindran. PG (M.D - DVL)

Department : Madras medical college. Ch-3

The request for an approval from the Institutional Ethical Committee(IEC) was considered on the IEC meeting held on 23rd September 2009 at 2.00P.M. in Madras Medical College, Deans, Chamber, Chennai-3. / Pharmacology seminar hall / madras medical college. Ch-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearnance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s).
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC,CHENNAI

CHAIRMAN
IEC MMC CHENNAI

21/10/09

DEAN
MADRAS MEDICAL COLLEGE
CHENNAI

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

லைகன் ப்லேனஸ் - ஹேலோபீட்டசோல், டாக்ரோலிமஸ் ஒரு ஒப்பீடு.

ஆராய்ச்சி நிலையம் : சரும நலத்துறை
அரசு பொது மருத்துவமனை
சென்னை — 600 003.

பங்கு பெறுபவரின் பெயர் :

பங்கு பெறுபவரின் எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கம் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்மந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை

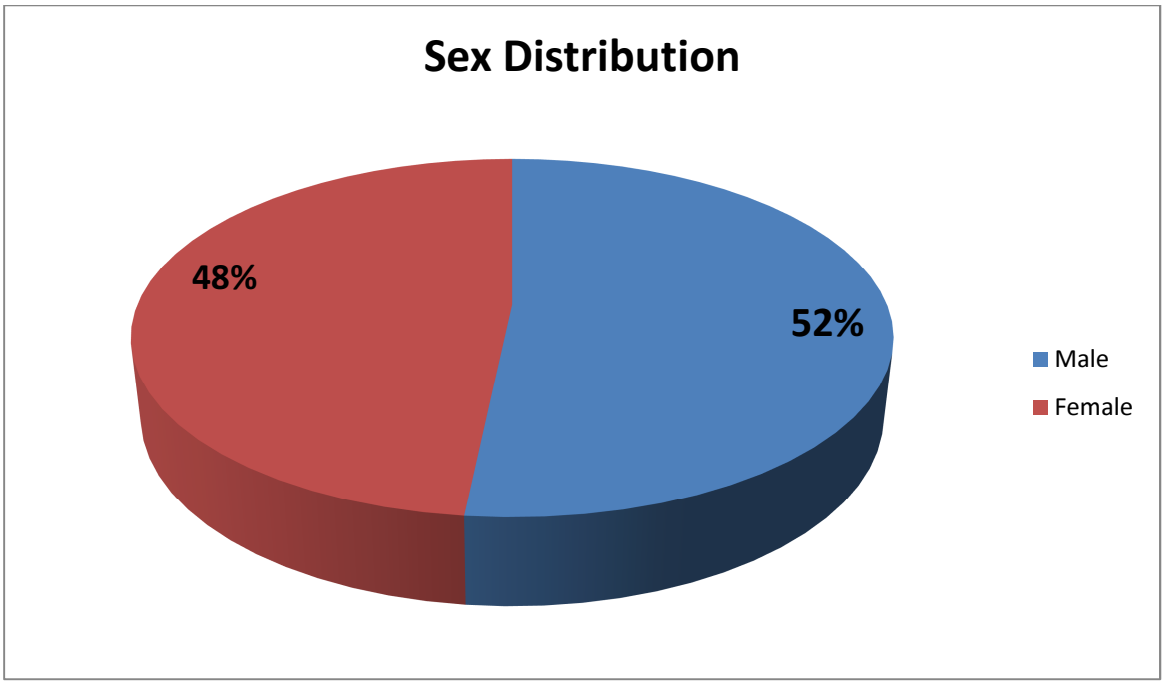
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

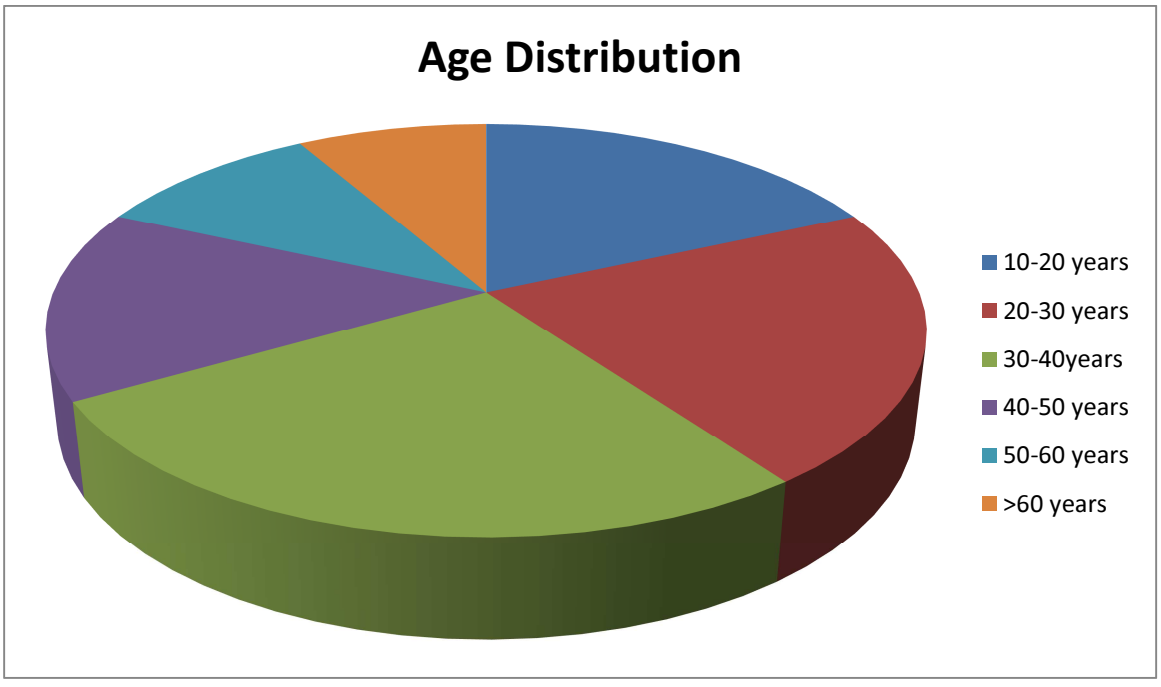
ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

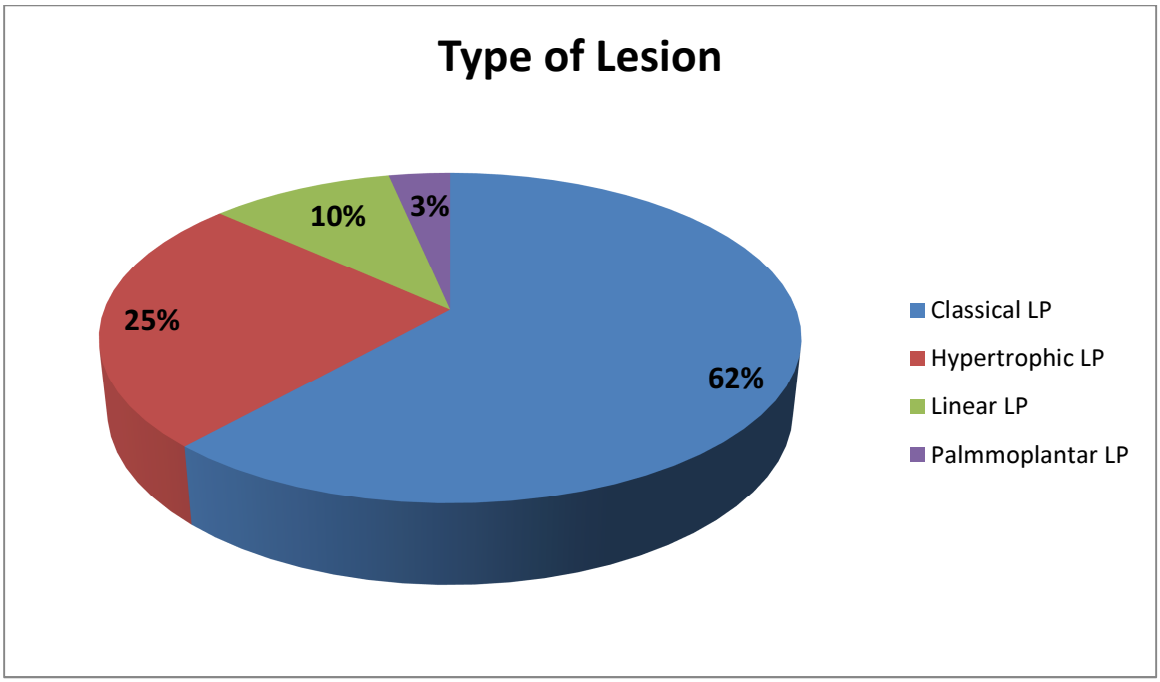
ஆய்வாளரின் பெயர் .....

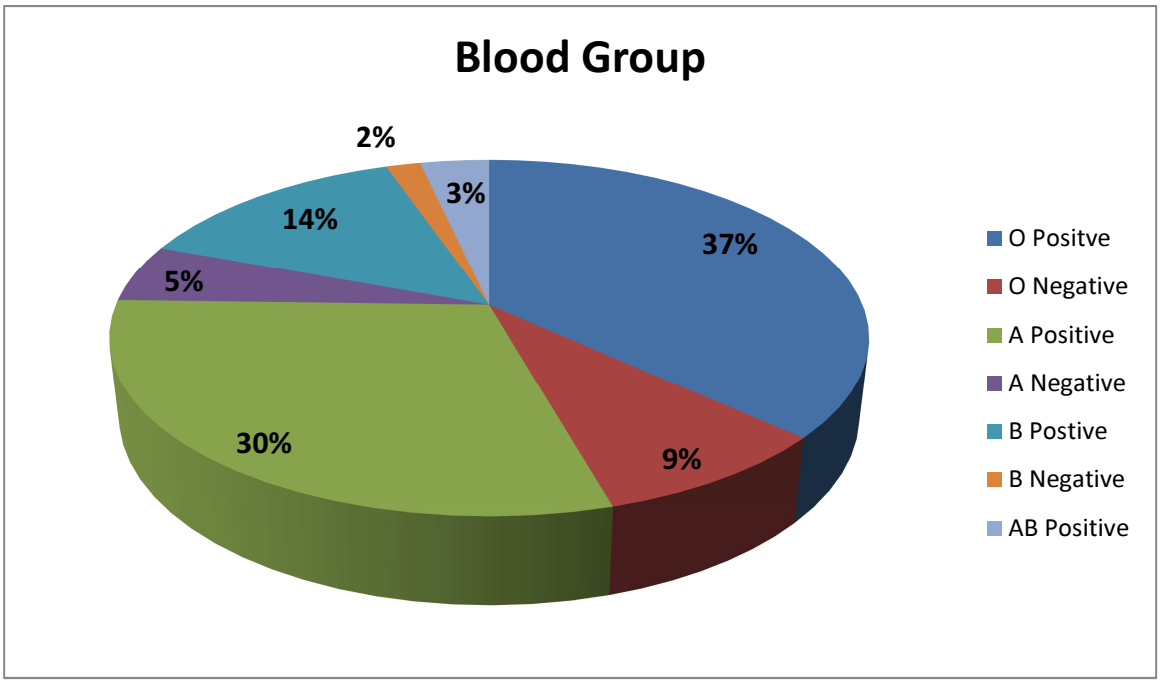
KEY TO MASTER SHEET

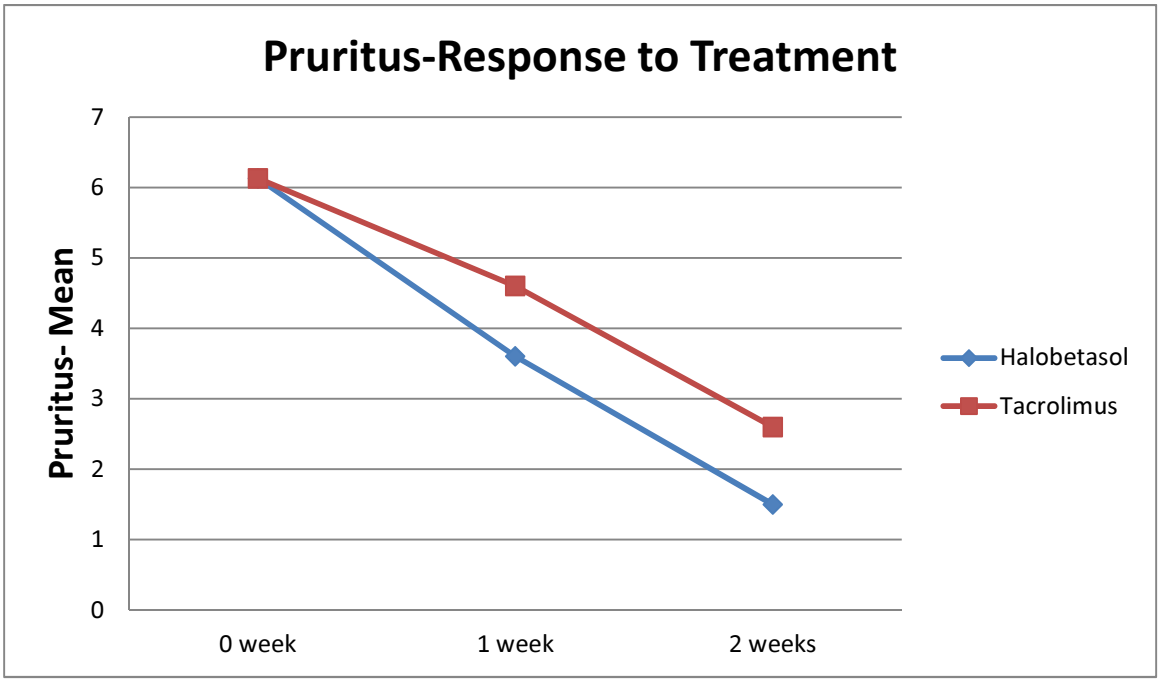
AA	Alopecia Areata
BLD GRP	Blood Group
bur	Burning
C	Classical
CLR	Cleared
DM	Diabetes Mellitus
DUR	Duration
E	Exposed
F	Female
fam	Family History
H	Halobetasol
HTN	Hypertension
HT	Hypertrophic
hypo	Hypopigmentation
L	Linear
LL	Lower Limb
M	Male
MAR	Marked Improvement
MOD	Moderate Improvement
mon	months
NE	Non-Exposed
NO CHG / NC	No Change
NL	New Lesions
P&S	Palms and Soles
REM	Remission
RE	Relapse
RESP	Response
side eff	side effects
skin dis	skin disorders
SLI	Slight Improvement
T	Tacrolimus
THK	Thickness
THR	Therapy
UL	Upper Limb
yrs	Years

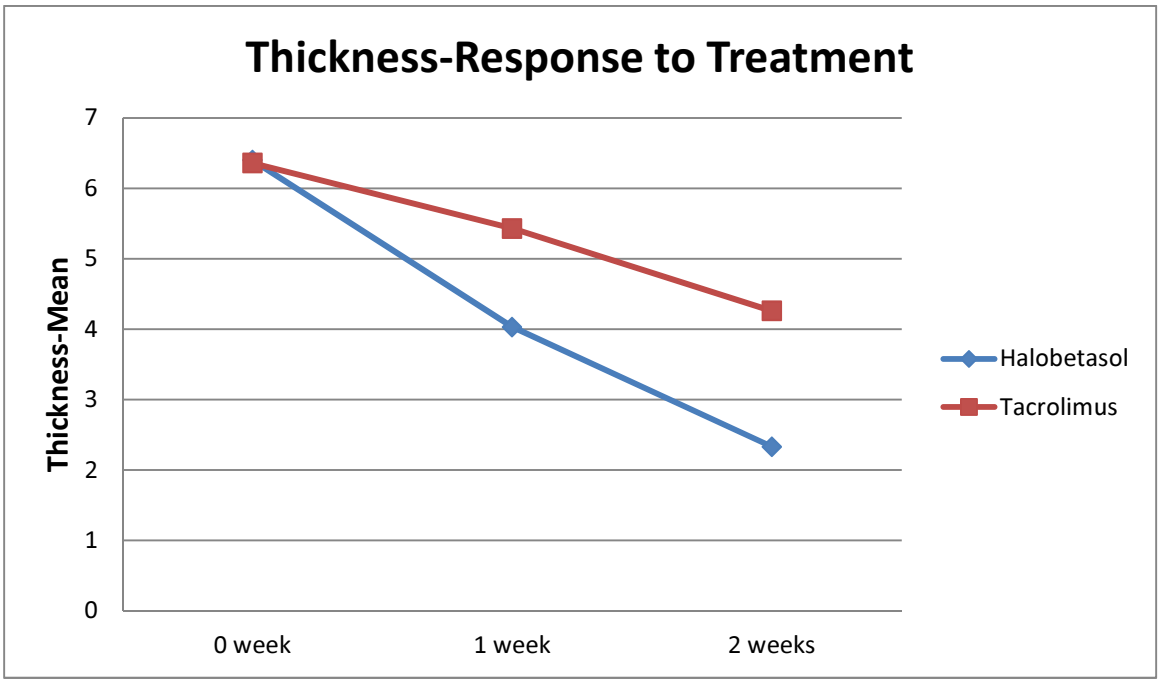

Sex Distribution
48%
52%
Male
Female

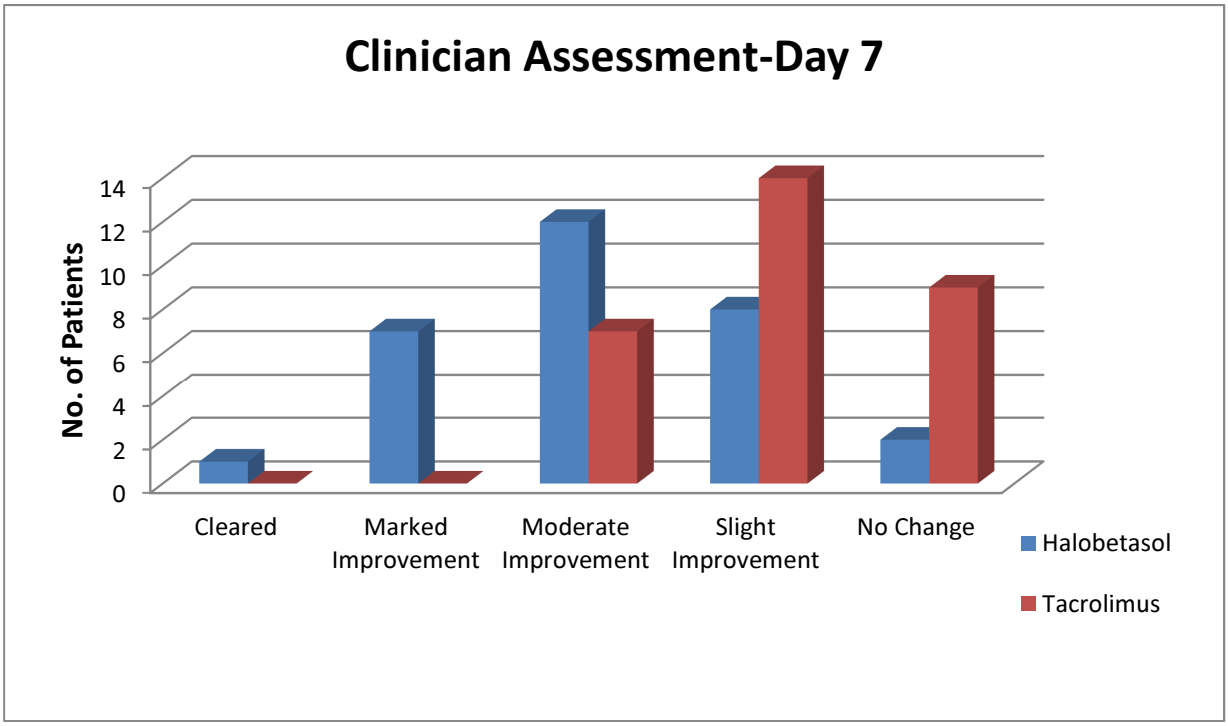

Age Distribution
10-20 years
20-30 years
30-40years
40-50 years
50-60 years
>60 years

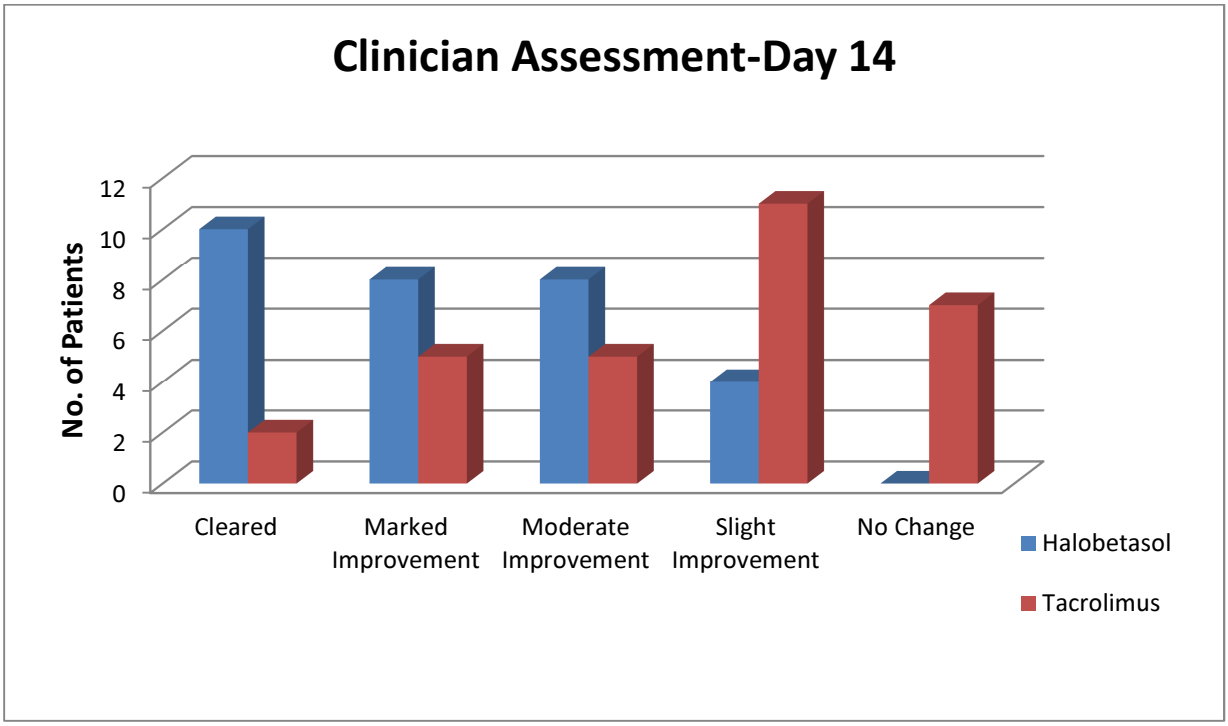

Type of Lesion
10%
3%
25%
62%
Classical LP
Hypertrophic LP
Linear LP
Palmmoplantar LP

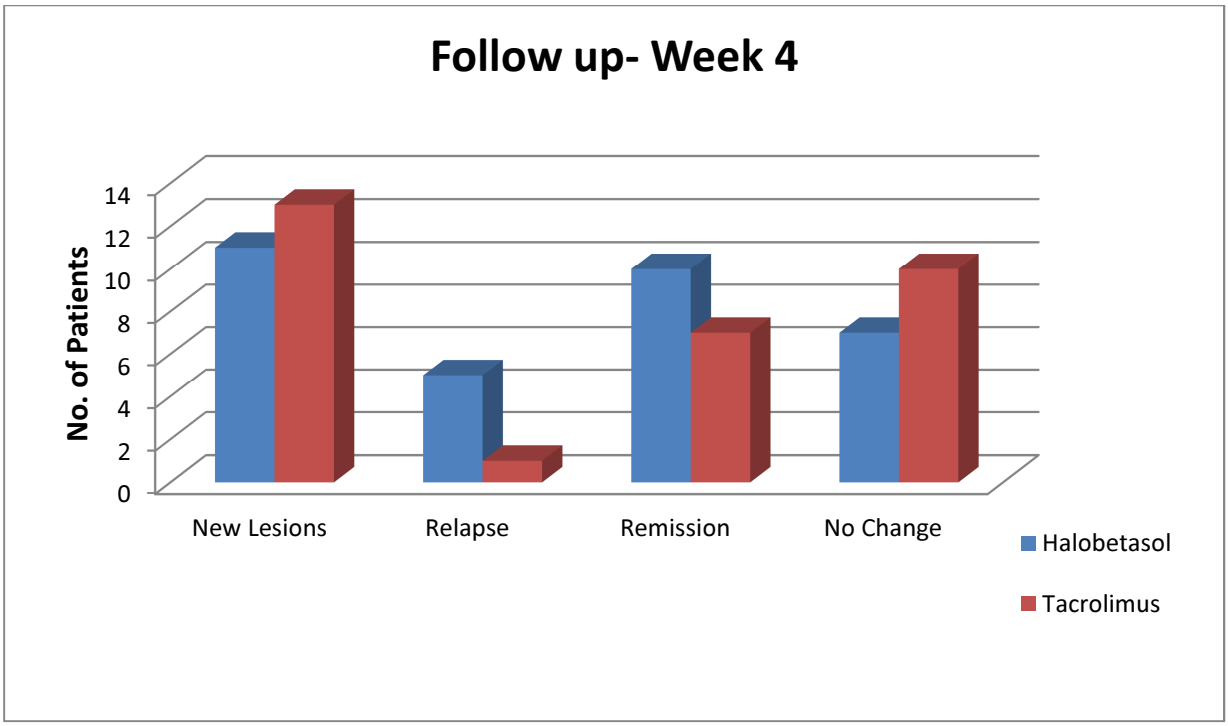

Blood Group
2%
3%
14%
37%
5%
30%
9%
O Positve
O Negative
A Positive
A Negative
B Postive
B Negative
AB Positive

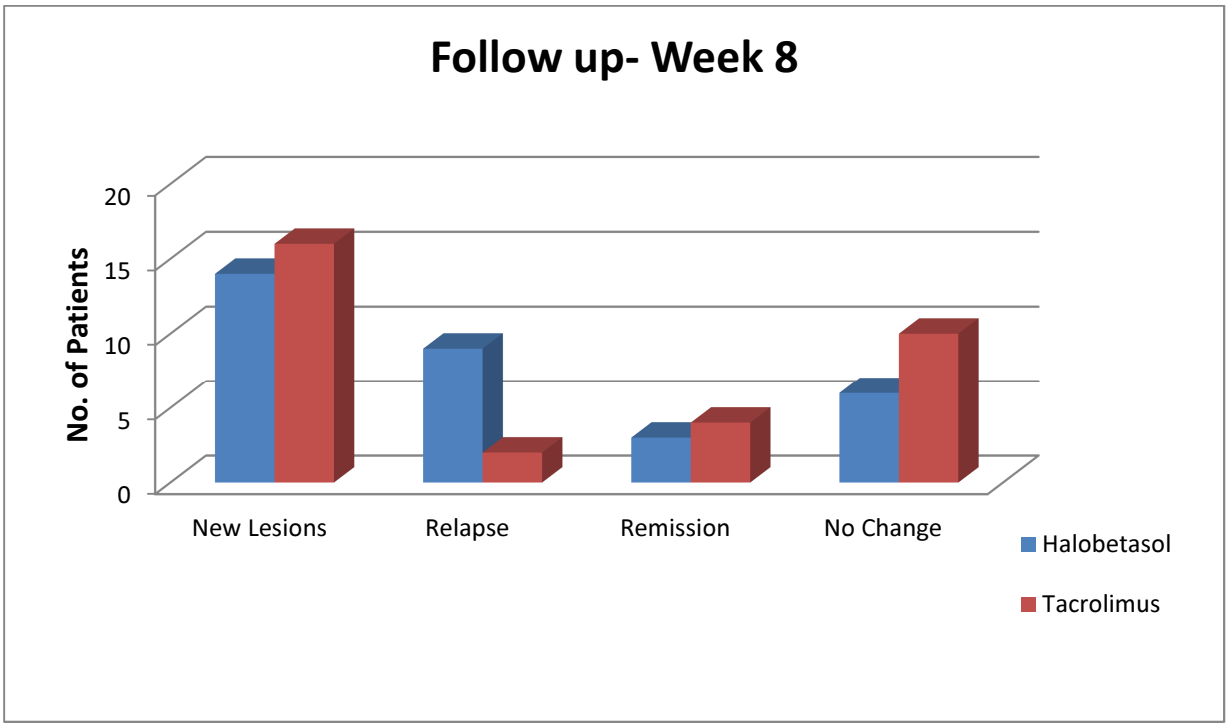

Pruritus-Response to Treatment
Pruritus- Mean
7
6
5
4
3
2
1
0
0 week
1 week
2 weeks
Halobetasol
Tacrolimus


Thickness-Response to Treatment
Thickness-Mean
7
6
5
4
3
2
1
0
0 week
1 week
2 weeks
Halobetasol
Tacrolimus


Clinician Assessment-Day 7
No. of Patients
14
12
10
8
6
4
2
0
Cleared
Marked Improvement
Moderate Improvement
Slight Improvement
No Change
Halobetasol
Tacrolimus


Clinician Assessment-Day 14
No. of Patients
12
10
8
6
4
2
0
Cleared
Marked Improvement
Moderate Improvement
Slight Improvement
No Change
Halobetasol
Tacrolimus


Follow up- Week 4
No. of Patients
14
12
10
8
6
4
2
0
New Lesions
Relapse
Remission
No Change
Halobetasol
Tacrolimus


Follow up- Week 8
No. of Patients
20
15
10
5
0
New Lesions
Relapse
Remission
No Change
Halobetasol
Tacrolimus

sl.no	SEX	AGE	BLD GRP	TYPE	SITE	DUR	E/NE	DM	HTN	famly h	THR	0 WEEK		1 WEEK			2 WEEK			1 MONTH				2 MONTHS				skin dis	side eff
												ITCH	THK	ITC	THK	RESP	ITCH	THK	RESP	RE	NL	NC	REM	RE	NL	NC	REM		
1	M	27	O +VE	HT	LL	1 yr	E	-	-	+	H	8	9	7	5	SLI	3	4	MOD	-	+	+	-	+	+	-	-	-	-
2	M	42	O +VE	C	LL	2 mon	UE	-	-	-	T	6	5	5	4	SLI	3	2	MOD	-	-	+	-	-	-	+	-	-	bur
3	F	62	O +VE	C	LL	1 mon	E	+	-	+	H	7	5	4	2	MOD	1	1	MAR	-	+	-	-	-	+	-	-	-	-
4	M	51	A +VE	C	UL	6 mon	UE	-	-	-	T	5	7	6	6	NO CHG	3	5	SLI	-	+	-	-	-	+	-	-	vitiligo	-
5	F	45	O +VE	C	LL	1.5 yrs	UE	-	-	-	H	6	6	2	3	MAR	0	0	CLR	-	-	-	+	+	-	-	-	-	hypo
6	F	40	AB +VE	C	LL	3 mon	UE	-	-	-	T	7	7	5	6	SLI	3	5	SLI	-	+	-	-	-	+	-	-	-	-
7	M	52	O -VE	HT	LL	2 yrs	E	-	-	-	H	9	9	8	8	SLI	4	5	MOD	-	-	+	-	-	-	+	-	vitiligo	-
8	F	69	A+VE	HT	LL	2 mon	E	-	-	-	T	9	9	9	10	NO CHG	7	7	SLI	-	+	-	-	-	+	-	-	-	bur
9	M	28	A+VE	HT	LL	1 yr	E	-	-	-	H	10	9	5	6	MOD	3	4	MOD	+	-	-	-	+	+	-	-	-	-
10	M	41	B+VE	C	UL	6 mon	UE	-	-	-	T	7	4	6	4	SLI	6	4	NO CHG	-	-	+	-	-	-	+	-	vitiligo	bur
11	M	15	AB +VE	P&S	P&S	6 mon	E	-	-	-	H	9	8	4	5	MOD	1	2	MAR	-	-	+	-	-	-	+	-	-	hypo
12	M	35	B+VE	C	LL	2 yrs	UE	-	-	-	T	7	7	6	7	NO CHG	5	7	NO CHG	-	-	+	-	-	-	+	-	-	-
13	M	18	A+VE	L	UL	4 mon	E	-	-	-	H	6	5	1	2	MAR	0	0	CLR	-	-	-	+	+	-	-	-	-	-
14	M	13	B+VE	C	UL	1 yr	E	-	-	+	T	7	7	6	6	SLI	2	5	SLI	+	-	-	-	+	-	-	-	-	bur
15	F	13	A+VE	C	LL	6 mon	E	-	-	-	H	4	5	1	3	MAR	0	0	CLR	-	-	-	+	-	+	-	-	-	-
16	F	51	A+VE	C	UL	3 mon	E	-	-	+	T	7	5	6	5	NO CHG	3	4	SLI	-	+	-	-	-	+	-	-	-	-
17	F	19	O+VE	C	UL	3 mon	UE	-	-	-	H	6	6	3	3	MOD	2	3	MOD	+	-	-	-	+	-	-	-	-	hypo
18	M	61	O+VE	HT	LL	1 yr	UE	-	-	-	T	6	10	5	10	SLI	3	10	SLI	-	-	+	-	-	-	+	-	-	-
19	M	14	A+VE	C	LL	3 weeks	E	-	-	-	H	5	7	2	4	MOD	1	2	MAR	-	+	-	-	-	+	-	-	-	hypo
20	M	36	O+VE	C	UL	2 mon	E	-	-	-	T	5	5	4	3	SLI	2	3	SLI	-	+	-	-	-	+	-	-	-	-
21	M	24	A+VE	C	UL	8 mon	E	-	-	-	H	4	6	3	5	SLI	0	0	CLR	-	-	-	+	-	+	-	-	-	hypo
22	M	28	O+VE	C	LL	2 weeks	E	-	-	-	T	2	5	1	4	SLI	0	0	CLR	-	-	-	+	-	-	-	+	-	bur
23	M	35	O+VE	C	CHEST	2 weeks	UE	-	-	-	H	7	3	0	0	CLR	0	0	CLR	-	-	-	+	-	-	-	+	-	hypo
24	F	21	O+VE	C	UL	1 mon	UE	-	-	-	T	6	5	3	3	MOD	3	1	MOD	-	+	-	-	-	+	-	-	-	bur
25	F	38	A+VE	C	LL	2 weeks	UE	-	-	-	H	6	7	3	1	MAR	0	0	CLR	-	-	-	+	-	-	-	+	-	hypo
26	F	23	AB+VE	C	LL	2 mon	E	-	-	-	T	6	4	3	2	MOD	1	0	MAR	-	-	-	+	-	-	-	+	-	-
27	F	45	O+VE	C	UL	2 mon	E	+	-	-	H	5	6	3	3	MOD	2	2	MOD	-	+	-	-	-	+	-	-	Vitiligo	-
28	F	28	A+VE	C	UL	1 mon	E	-	-	-	T	7	8	5	7	SLI	2	6	SLI	-	+	-	-	-	+	-	-	-	-
29	M	29	AB+VE	C	UL	3 mon	E	-	-	-	H	4	5	3	3	SLI	1	2	MAR	-	-	+	-	-	-	+	-	-	-
30	M	25	O+VE	L	LL	1 mon	UE	-	-	-	T	8	8	7	8	NO CHG	3	4	MOD	-	+	-	-	-	+	-	-	-	-
31	F	66	A+VE	C	UL	2 weeks	UE	+	-	-	H	3	5	1	1	MAR	0	0	CLR	-	-	-	+	-	+	-	-	-	-
32	F	39	O-VE	C	UL	20 days	E	-	-	-	T	2	2	1	1	MOD	0	0	CLR	-	-	-	+	-	-	-	+	-	bur
33	M	38	A+VE	HT	LL	6 mon	E	-	-	-	H	9	9	8	8	NO CHG	4	6	SLI	-	+	+	-	-	-	+	-	-	hypo
34	M	56	O+VE	C	LL	6 mon	UE	+	-	-	T	5	5	4	5	NO CHG	4	5	NO CHG	-	+	+	-	-	+	+	-	-	bur
35	F	35	AB+VE	HT	LL	2 mon	E	-	-	-	H	9	10	4	8	MOD	2	5	MOD	-	+	-	-	-	+	-	-	-	-
36	F	14	A+VE	HT	LL	8 mon	E	-	-	-	T	6	10	5	8	MOD	4	7	SLI	-	+	-	-	-	+	-	-	-	-
37	M	29	B+VE	HT	LL	3 mon	E	-	-	-	H	10	10	10	9	NO CHG	6	7	SLI	+	-	-	-	+	-	-	-	-	-
38	F	35	O+VE	C	LL	1 mon	E	+	-	-	T	8	6	3	4	MOD	0	3	MAR	-	-	-	+	+	-	-	-	-	-
39	F	25	O+VE	L	UL	2 mon	UE	-	-	-	H	2	5	0	2	MAR	0	0	CLR	-	-	-	+	-	+	-	-	-	-
40	M	45	B+VE	L	LL	3 mon	E	+	-	-	T	6	7	5	5	SLI	2	4	SLI	-	+	-	-	-	+	-	-	-	-
41	F	24	O+VE	C	TRUNK	1 mon	UE	-	-	-	H	6	5	3	2	MOD	1	1	MAR	-	+	-	-	-	+	-	-	-	-
42	F	29	A+VE	C	UL	1 mon	E	-	-	-	T	8	7	5	5	SLI	0	2	MAR	-	-	-	+	-	-	-	+	-	bur
43	F	40	O+VE	C	LL	3 mon	UE	-	-	-	H	5	5	3	2	MOD	1	1	MAR	-	+	-	-	-	+	-	-	-	hypo
44	M	20	A+VE	HT	LL	1.5 yrs	E	-	-	-	T	7	8	5	8	SLI	3	8	NO CHG	-	-	+	-	-	-	+	-	-	-
45	M	43	O-VE	C	UL	3 weeks	E	-	-	-	H	1	3	0	1	MAR	0	0	CLR	-	-	-	+	-	-	-	+	-	-
46	M	32	O+VE	L	UL	4 mon	E	-	-	-	T	4	5	2	3	MOD	0	1	MAR	-	-	-	+	-	+	-	-	-	-
47	M	46	B-VE	C	UL	9 mon	E	-	-	-	H	3	4	1	4	MOD	0	1	MAR	-	+	-	-	-	+	-	-	-	-
48	F	43	A-VE	HT	LL	2 mon	UE	-	-	-	T	10	9	9	9	NO CHG	5	9	NO CHG	-	-	+	-	-	-	+	-	-	bur
49	M	35	O+VE	C	LL	2 mon	UE	-	-	-	H	5	5	3	3	MOD	2	2	MOD	+	+	-	-	+	-	-	-	-	hypo
50	F	32	A+VE	C	TRUNK	1.5 yrs	E	-	-	-	T	4	6	4	6	NO CHG	2	6	NO CHG	-	-	+	-	-	-	+	-	-	-
51	M	36	B+VE	HT	LL	1.5 yrs	E	-	-	-	H	9	10	8	7	SLI	1	7	MOD	-	-	+	-	-	-	+	-	AA	-
52	M	32	O-VE	C	UL	1 mon	E	-	-	-	T	6	5	1	4	MOD	1	2	MAR	-	-	-	+	-	+	-	-	-	-
53	F	18	O-VE	C	UL	7 mon	E	-	-	-	H	5	6	4	4	SLI	0	2	MAR	-	+	-	-	-	+	-	-	-	-
54	M	17	O+VE	HT	LL	1 yr	E	-	-	-	T	10	9	7	9	SLI	5	8	SLI	-	-	+	-	-	-	+	-	-	bur
55	F	57	B+VE	HT	LL	6 mon	E	-	-	-	H	8	8	7	7	SLI	4	6	SLI	+	-	-	-	+	-	-	-	-	-

56	M	55	O+VE	P&S	P&S	3 mon	E	-	-	-	T	5	5	4	3	SLI	2	2	MOD	-	+	-	-	-	+	-	-	-	-
57	F	34	A-VE	C	LL	2 mon	E	-	-	-	H	5	4	0	2	MOD	0	0	CLR	-	-	-	+	+	-	-	-	-	hypo
58	F	59	O+VE	C	TRUNK	2 mon	UE	+	-	-	T	6	6	5	4	SLI	3	2	MOD	-	+	-	-	-	+	-	-	-	-
59	F	43	A-VE	HT	LL	2 mon	UE	-	-	-	H	8	9	7	8	SLI	6	7	SLI	-	-	+	-	-	-	+	-	-	-
60	F	17	B+VE	L	UL	5 mon	E	-	-	-	T	2	4	2	4	NO CHG	2	4	NO CHG	-	-	+	-	-	+	+	-	-	bur